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Original Research Article

In vivo study of naringin-loaded biomaterials patch coupled with biosensors for diabetic foot ulcer management

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are a severe complication of diabetes, often leading to prolonged hospitalizations and even amputations. The need for advanced, efficient treatments is critical, particularly in regions like Indonesia, where healthcare resources are limited. In this study, naringin, a bioactive flavonoid renowned for its antioxidant and anti-inflammatory properties, was embedded within a biocompatible matrix of alginate, mesoporous silica, and polyvinyl alcohol.
Methods: This patch was engineered using electrospinning techniques, ensuring a controlled release of naringin to the wound site. To further advance this treatment modality, a colorimetric biosensor targeting uric acid a critical biomarker of wound severity was seamlessly integrated into the patch. *In vivo* studies were conducted using diabetic mouse models to assess the patch's efficacy in promoting wound healing.
Results: The results were promising: the naringin-loaded patches significantly accelerated wound closure and improved tissue regeneration compared to standard treatments. However, while the concept of integrating biosensors showed promise, the biosensor component in this study did not perform optimally and requires further refinement. The current iteration of the biosensor provided limited real-time monitoring capability, indicating the need for enhanced sensitivity and reliability for the application in the wound environment. This study highlights the potential of naringin-infused biomaterials as a therapeutic option for DFU treatment and underscores the importance of ongoing research to optimize biosensor integration.
Conclusions: While the *in vivo* results are promising, the study calls for further development of biosensors to fully realize the potential of this combined approach in clinical settings.

Keywords: Diabetic foot ulcer, Alginate, Biomaterial, Biosensor, Naringin

INTRODUCTION

Diabetes is characterized by metabolic abnormalities in blood glucose due to decreased insulin effectiveness. Hyperglycemia, or high blood sugar levels, is a primary symptom, significantly affecting morbidity and mortality rates.[1,2] Since 2012, diabetes has contributed to 2.2 million deaths globally. By 2016, it caused 1.6 million deaths annually, with a 5% increase in mortality from 2000 to 2016.[3] In Indonesia, over 19 million adults suffer from diabetes, with a prevalence rate of 10.8%.[4] While hyperglycemia can be managed with oral medications and insulin injections, complications like diabetic foot ulcers (DFUs) remain a significant challenge, especially in developing countries like Indonesia. Socioeconomic and educational barriers hinder effective management despite national health insurance programs. DFUs result from poor vascularization, leading to ischemia and necrosis, and

peripheral neuropathy, increasing the risk of unnoticed lesions.[5,6] Diabetes impairs wound healing through oxidative stress, impaired angiogenesis, and reduced immune response.[7] Additionally, Indonesia's tropical climate exacerbates these issues by promoting bacterial and fungal infections.[8] Untreated DFUs risk leading to amputation. The Indonesian Ministry of Health provides guidelines for diabetes and DFU treatment, focusing mainly on physical therapies like lasers and electrostimulation.[9] However, these treatments are often impractical due to limited healthcare infrastructure, resulting in suboptimal outcomes.[10]

Biomaterials, which are compatible with biological systems, are extensively used in medical devices, including implants and drug delivery systems. Research aims to identify both natural and synthetic materials with medical applications. Biomaterials are critical in wound care, with substances like gelatin, pectin, chitosan, polyethylene glycol, carboxymethylcellulose, polyurethane, and alginate being investigated for diabetic wound dressings.[11,12] Alginate, derived from brown algae, is notable for its ability to form hydrogels through ion crosslinking, enhancing its mechanical properties and making it ideal for drug delivery systems.[13,14]

Naringin, a compound from citrus plants, is known for its antidiabetic and wound healing properties, exhibiting anti-inflammatory and antioxidant effects that reduce pro-inflammatory cytokines and promote growth factors essential for tissue repair and angiogenesis.[15-18]

Biosensors, which detect biomarkers from the body, are used as diagnostic tools for various diseases or physiological processes. Certain biosensors, like brilliant yellow and anthocyanins, detect wound pH, while the 4-AAP/TOPS reagent combination detects uric acid in wounds. The colorimetric changes produced by these biosensors serve as indicators of wound severity and healing progress. This study focuses on a biosensor detecting uric acid, which is elevated in wounded skin compared to normal skin and increases with wound severity, making it a reliable biomarker for assessing wound conditions.[19,20] The 4-AAP/TOPS compound aids in the indirect detection of uric acid by reacting with hydrogen peroxide, a byproduct of uric acid breakdown, to produce a purple complex. The intensity of this colorimetric response correlates with the uric acid concentration, providing a visual measure of wound severity.[21,22]

Biomaterials integrated with biosensors offer a promising alternative for DFU treatment, providing patients with effective home-based care options. Although Indonesian researchers have made progress in developing biomaterials, biosensor development lags behind, and biomaterials have not been widely adopted for industrial and commercial use.[12,23] Given the non-fatal nature of DFUs and the availability of alternative treatments, this area has not been prioritized by the government and pharmaceutical companies. This research aims to develop a smart biomaterial-based patch combined with a biosensor to assess wound closure in mice, providing data for an industry-ready herbal patch for DFU treatment in Indonesia.

METHODS

This research is a laboratory experimental study conducted in The Faculty of Medicine and Health Science, Atma Catholic University of Indonesia from August 2023 to June 2024. The materials: Sodium Alginate (low viscosity) was purchased at Sisco Research Laboratories (Mumbai, India). while other materials were bought from Sigma-Aldrich. Materials were used without further purification. Animal trials were conducted in this research using male ddY mice approved by The Ethical Committee of Faculty of Medicine and Health Science, Atma Jaya Catholic University permits number 22/10/KEP-FKIKUAJ/2023.

Patch fabrication

Patches were fabricated using the electrospinning technique at Atma Jaya Catholic University of Indonesia. The formulation consisted of 2.8% alginate, 2.4% polyvinyl alcohol (PVA), 0.25% mesoporous silica, and 5% naringin as the active wound healing agent for diabetic wounds, optimized based on the studies reported by Okur et al.[17] The patches were sterilized via 96% ethanol washing followed by UV irradiation to ensure sterility without compromising structural integrity and therapeutic efficacy.

Physical and chemical characterization

Patch characteristics were evaluated starting from organoleptic properties (structure, color, shape, and odor) using standard laboratory techniques. Thickness and uniformity were measured using a micrometer and an analytical balance. Moisture content tests were performed by pre-drying patches in a desiccator for 24 hours, then exposing them to ambient humidity for another 24 hours. The moisture absorption was calculated as given in the equation.

$$Mos\% = \left[\frac{(w2 - w1)}{w1}\right] \times 100$$

Where Mos% is the patch moisture percentage, W_1 is the weight of pre-exposed patch, and W_2 is the weight of exposed patch.

Fold endurance was assessed by repeatedly folding the patch at the same point until failure, recording the number of folds achieved. Absorption capacity was tested in both water and simulated body fluid; patches were weighed dry, submerged, then reweighed wet. Absorption percentage was calculated as given in the equation.

$$Abs\% = \left[\frac{(w2 - w1)}{w1}\right] \times 100$$

Where Abs% is the patch absorption percentage, W_1 is the weight of dry patch, and W_2 is the weight of wet patch.

Drug migration and release studies

Naringin migration from the patch matrix was quantified by immersing the patch in distilled water for 15 minutes and measuring the release concentration via UV-visible spectrophotometry against a standard naringin solution. The casting method is done by pouring the formula solution into a petri dish, dried, and soaked in 3% $CaCl_2$ solution.

Animal testing

Animal trials were conducted using laboratory mice over eight days. Patches were applied to diabetic wound models in rodents, with daily monitoring and photographic documentation before and after application. ImageJ software was used to assess the wound area and biosensor signal intensity. Then the statistical analysis was done using JASP to determine the significant difference from the data. The blood plasma of each treatment group was also evaluated for MMP-2 and MMP-9 activity using gelatin zymography.

RESULTS

Fabrication and physical evaluation of patches

The alginate/meso-silica/naringin patches were fabricated successfully. The resulting patches were produced in long sheets, which were then cut to the required sizes as shown in Figure 1. The microscopic texture of the patches reveals well-formed fibers created through electrospinning, along with a surface morphology characterized by a hollow topography. The formulated patches exhibited satisfactory physical characteristics based on the evaluation parameters listed in Table 1. The physical characteristics of the patches remained unchanged after sterilization with UV radiation.

The release of naringin from the alginate patch matrix was confirmed using a simple method of immersing the cut patches in distilled water. This was done to ensure that the drug could be effectively released from the matrix to the skin. The comparison of spectra in Figure 2 shows a close resemblance, indicating that naringin can successfully migrate from the patch matrix to the wound. The maximum wavelength for naringin is observed at 282 nm. The rough profile of the naringin release rate from the alginate/meso-silica/PVA patch matrix was also evaluated. The release data, visualized in Figure 2, show that the absorbance of naringin at 282 nm continues to increase from 5 minutes to 24 hours of application. This indicates that the matrix formulation can provide a controlled release effect of naringin.

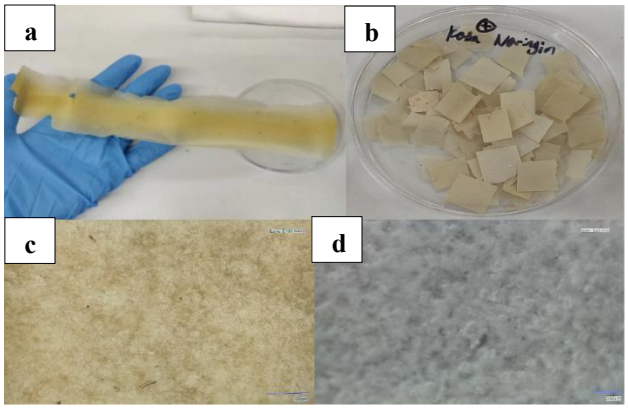

Figure 1: Macroscopic evaluation of (a) collected patch, (b) cut patch, and its microscopic visualization of the patch (c) normal mode, and (d) OP SEM mode.

Wound healing evaluation

The wound healing evaluation demonstrated a significant reduction in wound area in the group treated with naringin-infused patches compared to the other groups (Table 2 and Figure 3). The naringin patches outperformed both the non-naringin patches and the negative control, highlighting the effectiveness of naringin as an active wound-healing agent. These findings were further supported by the histology observation (Figure 4) where the negative control group could be seen in an inflammation phase with a lot of immune cells in the tissue. This result contrasts with the positive commercial patch and naringin patch which showed the differentiation of fibroblast with hair follicle and sebaceous glands formation, while the non-naringin patch showed slower healing progression. Gelatin zymography analysis (Figure 5), showed additional data suggesting that mice treated with the naringin patch tends to express MMP-2 instead of MMP-9. This suggests that the wound healing process was in the remodeling phase rather than the inflammation phase, which is the opposite of what was observed in the negative control group.

Table 1: Physical evaluation parameter comparison of patches.

Evaluation parameter	Alginate/meso-silica/naringin	Alginate/meso-silica	Commercial patch
Fold endurance (folds)	18	26	50
Thickness (mm)	0.07	0.095	0.19
Weight (size 1×1) (grams)	0.009	0.013	0.005
Moisture percentage (%)	0	0	0

Continued.

Evaluation parameter	Alginate/meso-silica/naringin	Alginate/meso-silica	Commercial patch
Fluid absorption percentage (%)			
Water	557.142	558.557	1595.13
SBF	345.745	388.291	1125.67
Organoleptic characteristics	Yellowish, opaque, odorless, slightly rough	White, slightly transparent, odorless, smooth	White, opaque, odorless, smooth

Table 2: Average wound area (cm^2) of the treatment group result per day.

Day	Negative control (-)	Commercial patch	Alginate/meso-silica without naringin patch	Alginate/meso-silica/naringin patch
0	0.64525	0.5975	0.62525	0.54775
1	0.56325	0.42325	0.56375	0.5205
2	0.67225	0.327	0.55825	0.5225
3	0.898	0.42425	0.59625	0.3975
4	0.75225	0.47175	0.4795	0.466
5	792.469	0.36825	0.36475	0.317
6	0.63675	0.42025	0.41975	0.264
7	0.40675	0.34175	0.30175	0.286
8	0.64525	0.5975	0.62525	0.54775

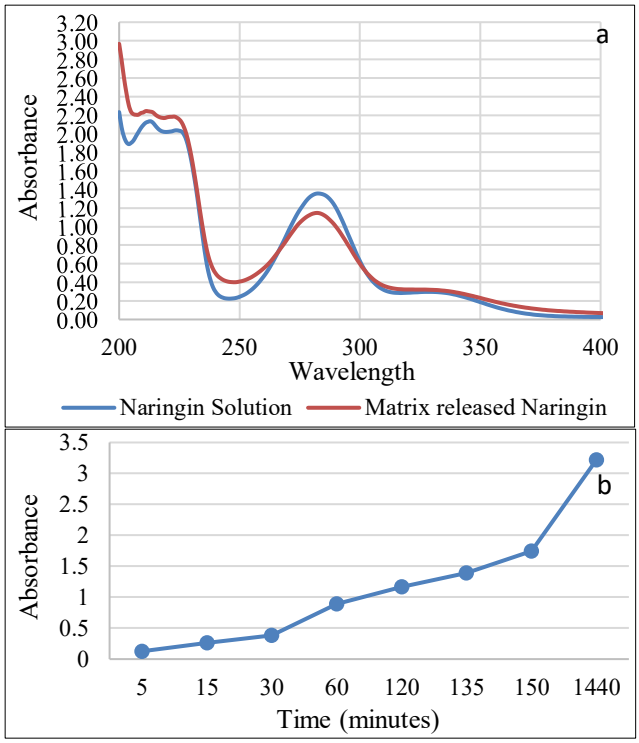

Figure 2: Spectrophotometry data (a) comparison of UV-vis spectra between the standard naringin solution and the naringin release from the patch matrix, and (b) naringin release rate from the patch matrix.

Biosensor evaluation

The biosensor evaluation data was represented in Table 3 and visualized in Figure 6. Based on the average mean gray value, the data demonstrated a linear Spearman correlation (Table 4) between the naringin patch wound area and the mean gray value (p value=0.002). While the non-naringin patch doesn't give a significant correlation (p value=0.183). However, these results indicate that the biosensor is not yet optimized for wound healing detection. Ideally, as the wound closes and the area decreases, the mean gray value should inversely increase, reflecting the reduction in wound severity.

Table 3: Average mean gray value of the treatment groups per day.

Day	Alginate/meso-silica without naringin patch	Alginate/meso-silica/naringin patch
0	99.555	146.8725
1	94.69	127.7775
2	70.3425	139.5925
3	66.9425	98.755
4	73.105	96.9925
5	73.335	107.9175
6	57.54	67.885
7	57.715	84.67
8	99.555	146.8725

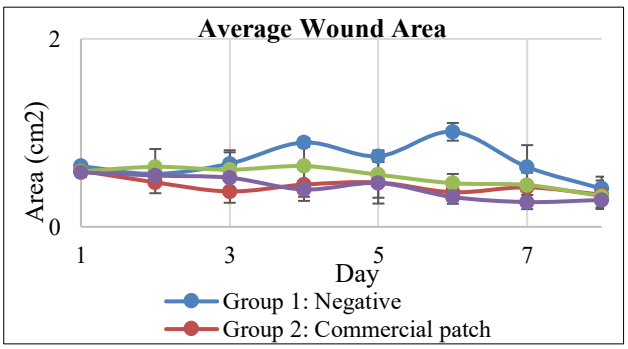

Figure 3: Comparison of the average wound area for each treatment group.

Table 4: Spearman correlation test between patch's wound area and mean gray value.

Group	Spearman Rho	P value	Interpretation
Group 3: non-naringin	0.524	0.183	Moderate positive correlation; not statistically significant
Group 4: naringin	0.905	0.002	Strong positive correlation; statistically significant

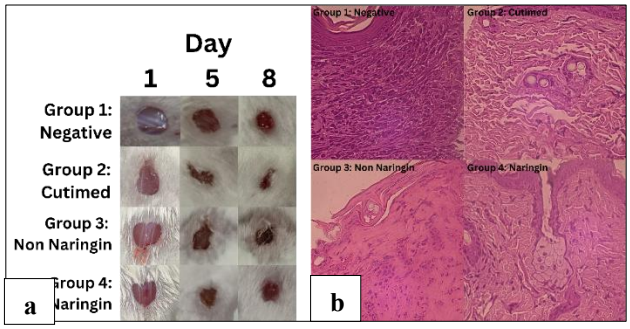

Figure 4: (a) Wound healing progression in each group, and (b) would healing histology on day 8.

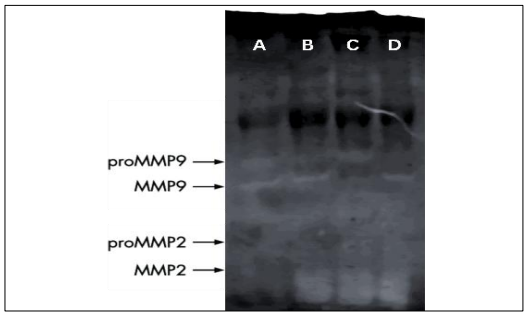

Figure 5: MMP activity evaluation using gelatin zymography method (A) negative group, (B) commercial patch, (C) non-naringin patch, and (D) naringin patch.

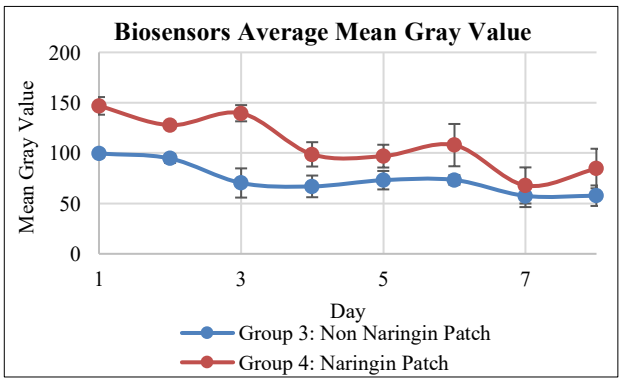

Figure 6: Average mean gray value of the treatment groups per day.

Table 5: Naringin patch cost estimation table.

Ingredient/ process	Quan -tity	Unit price (IDR)	Total cost (IDR)
Full patch			
Alginate	28 g	375,000/kg	10,500
PVA	24 g	150,000/kg	3,600
Mesoporous silica	2.5 g	1,500,000/kg	3,750
Triton X-100	10 ml	750,000/l	7,500
Naringin	50 g	3,000,000/kg	150,000
HRP	0.1 g	3,000,000/g	300,000
Uricase	0.1 g	4,500,000/g	450,000
4-AAP	1 g	1,500,000/kg	1,500
TOPS	1 g	7,500,000/kg	7,500
Electrospinning		750,000	750,000
UV sterilization		150,000	150,000
Total cost (full patch)			1,834,350
Cost per patch (full)	1 kg/ 67 patches		27,386

DISCUSSION

The fabrication of the alginate/meso-silica/naringin patches using the electrospinning method yielded better physical characterization compared to the more conventional solvent casting method.[24,25] The yellowish hue of the patches is due to naringin, a fine yellowish powder. Currently, there are no national or international standards for testing dermal patches. However, some publications have used parameters similar to those in this study for evaluating the physical and mechanical properties of patches.[26,27]

The prototype patches in this study consist of three components: the alginate/meso-silica/PVA matrix, the natural active compound naringin, and the 4AAP/TOPS biosensor. This design offers a different approach compared to commercial patches like, which mainly an alginate matrix that are primarily used to control the moisture level in diabetic wounds.[28] The porous structure in the patch matrix contributed by mesoporous silica, provides a better controlled release properties for the naringin up to 24 hours of application.[29] The alginate/meso-silica/PVA patches with naringin aim to control wound moisture while releasing naringin to reduce excessive inflammation in diabetic wounds.[18] While the 4AAP/TOPS biosensor is added to help detect the severity of the wound to predict its healing time.

Significant differences were observed between the alginate/meso-silica/naringin patches, alginate/meso-silica patches without naringin, and a commercial patch. The incorporation of different materials resulted in variations in physical properties. Patches containing naringin showed lower values in fold resistance, thickness, weight, and fluid absorption compared to those without naringin. The reduced density in naringin-containing formulations

suggests that naringin increases matrix porosity, making the patches less dense but more porous. The increased porosity may enhance the patch's controlled release properties, but the chemical nature of naringin reduces patch's hydrophilicity, negatively impacting fluid absorption, as shown by the data.[30]

Naringin was chosen for this study to demonstrate its healing effectiveness as a single isolate and its compatibility with the patch matrix. Although isolated compounds are generally more expensive due to extensive purification processes, using citrus peel extract as an alternative could reduce production costs while maintaining the therapeutic benefits.[31] A cost comparison and commercialization viability analysis (Table 5) indicated that the prototype patches could be a cost-effective alternative in the Indonesian market. The estimated production cost for the prototype patches was Rp. 27,386.00 per patch, compared to Rp. 125,000.00 for the commercial patches. This estimate does not yet account for potential cost reductions from mass production or profit margins.

Fluctuations in wound area were observed, leading to varying healing rates that did not consistently decrease. This variation is likely due to inflammation, which may have been caused by infection or the diabetic condition of the mice. Inflammation can influence the expression of cytokines and other pro-inflammatory molecules, increasing oxidative stress and hindering the wound healing process.[32,33] The replication data also showed noticeable variation across groups, with the negative control group exhibiting the least variation. In contrast, the treatment group using the naringin patch showed higher variability, largely due to the patch's adhesion capability.[34] The unpredictable activity of the mice often led to the patch detaching, resulting in inconsistent wound contact and varying amounts of naringin being delivered to the wound. Additionally, individual biological differences among the mice contributed to this variability.

The naringin patch was effective in promoting wound healing compared to the negative control and the patch without naringin. The naringin-alginate prototype patch likely accelerates wound healing by regulating collagen synthesis, similar to commercial alginate patches.[35] However, its lower absorption profile results in slightly different moisture control. Nonetheless, the inclusion of naringin, a herbal biomaterial, demonstrates significant potential in enhancing diabetic wound healing by its antioxidant and antidiabetic properties.[18,36] This highlights the broader potential for incorporating herbal materials into medical formulations, encouraging further exploration and development in this area.

The biosensor evaluation revealed a linear correlation between mean gray value and wound area, rather than the expected inverse relationship. This suggests that the biosensor may not accurately capture the dynamics of wound healing, indicating a need for further improvement in its design and functionality. Factors contributing to this issue may include interference from wound tissue or the patch matrix, insufficient time for the colorimetric reaction, and potentially low levels of uric acid biomarkers detectable by the biosensor.[37,38] The absence of uric acid level measurements in mice adds uncertainty to the results, and environmental factors such as temperature and pH could also affect the biosensor's performance.[37,39,40]

This study has several limitations. First, the animal model used may not fully replicate the complex physiological conditions of human diabetic foot ulcers, which involve multifactorial systemic and local factors. Second, while the biosensor showed a correlation with wound area, its colorimetric response was not yet optimal or consistent enough for reliable wound monitoring, indicating a need for further refinement. Third, variability in patch adhesion due to animal activity affected the uniformity of drug delivery and may have influenced wound healing outcomes. Lastly, the short study duration may not capture long-term healing dynamics or potential adverse effects. Future studies should involve longer observation periods, improved biosensor calibration, and preclinical trials in larger animals or human models to better evaluate efficacy and usability.

CONCLUSION

This study successfully developed a novel alginate-based patch infused with the herbal compound naringin and integrated with a biosensor for DFU treatment. The naringin patch showed promising results in accelerating wound healing in diabetic mice, demonstrating its potential as a cost-effective and accessible alternative for DFU management in Indonesia. However, the biosensor requires further refinement to enhance accuracy and reliability. The findings highlight the potential of integrating herbal medicine into advanced wound care, encouraging future research to optimize the patch's properties and biosensor functionality for clinical application.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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