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Submission date: 12-Aug-2022 09:58PM (UTC+0700)

Submission ID: 1881782066

File name: 2022_JAPS,_Besse_Yuliana.pdf (4.13M)

Word count: 5745

Character count: 29925



Wound healing effect of snakehead fish (*Channa striata*) mucus containing transdermal patch

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ARTICLE INFO

Received on: 07/11/2021
Accepted on: 10/05/2022
Available Online: 05/07/2022

Key words:

Patch, albumin, diabetic ulcers, snakehead fish, wound healing, mucus.

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ABSTRACT

Snakehead fish (*Channa striata*) has a high albumin content which contributes to the formation of new tissues in wound healing. The purpose of this study was to develop and evaluate the patch for transdermal delivery containing albumin from snakehead fish mucus in wound healing of diabetic Wistar rats (*Rattus norvegicus*). The albumin content in the snakehead fish mucus was analyzed by UV-Vis spectrophotometry. The patch was formulated by three different snakehead fish mucus extracts (1%, 3%, and 5%), and their physicochemical properties were determined. Wound healing was evaluated toward normal and diabetic rats. All data were analyzed by statistical analysis. The results showed that albumin content in the mucus extract was 27.73 µg/l. Organoleptic properties evaluation showed a brown color patch with a smooth surface and homogeneous weight. The pH and moisture were within the requirement of the patch. The activity of the positive control group, formula F(+), showed no significant difference from the action of formula F3 on the eighth day of treatment. These data indicate that the formulation of patch transdermal containing snakehead fish mucus extract is prominent to be developed for the wound healing treatment of diabetic ulcers.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia. DM can occur due to impaired insulin secretion or increased cell resistance to insulin (ADA, 2009). The World Health Organization noted that, in 2019, around 1.5 million deaths were directly caused by diabetes. Another 2.2 million deaths in 2012 were due to high blood glucose levels (WHO, 2021). The increase in diabetes cases is difficult to overcome due to inadequate DM therapy management. The treatment of DM is only to decrease the blood glucose levels, not to treat DM completely (Adu *et al.*, 2019). Thus, DM complications continue to develop, one of which is diabetic foot ulcer (DFU) in 15–25% of the total DM patients (Yazdanpanah *et al.*, 2018). DFU manifests diabetic neuropathy

due to decreased blood perfusion to the periphery, causing tissue necrosis and peripheral ischemia (Alexiadou and Doupis, 2012; Volmer-Thole & Lobmann, 2016).

Since DFU is associated with the leading cause of morbidity and mortality in DM, effective treatment for DFU patients is needed. Wound care in DFU patients requires special handling not to cause infection and the risk of amputation (Everett and Mathioudakis, 2018). Diabetic ulcer dressing conventionally cleans the wound using normal saline or 0.9% NaCl solution, added with povidone-iodine, and wrapped with dry gauze to protect and prevent infection. However, using this method has several risks, including the gauze becoming dry and sticking to the wound and causing pain, and the new cells will also be damaged. Previous studies have exhibited that the development of wound care methods and wound dressings has shifted to the modern approach, such as alginate dressing, foam dressing, and hydrogel (Dumville *et al.*, 2013; Saco *et al.*, 2016). However, these methods should be controlled of humidity because it contributes to wound healing. Besides, less humid conditions will cause cell death and no matrix tissues are formed.

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Nowadays, natural products derived from animals, minerals, and plants are relatively safe if the chemical content is determined. Therefore, the utilization of natural resources, including aquatic biota, has been widely studied for active component exploration (Fawwaz *et al.*, 2018; 2019). One source of medicinal ingredients derived from animals is snakehead fish (*Channa striata*) which contains amino acids and albumin, and other bioactive ingredients that play a role in wound healing (Rahayu *et al.*, 2016). Snakehead fish is a source of protein that has been used empirically in wound healing (Sahid *et al.*, 2018). This fish lives in the river, especially in Indonesia. The snakehead fish mucus contains essential amino acids, including arginine, glycine, lysine, proline, glucosamine, D-glucuronic acid, and carnosine which are needed to heal wounds (Baic and Sheikh, 2000). Arginine is the sole precursor of nitric oxygen, a molecular signal involved in the immune response, angiogenesis, epithelialization, and tissue formation (Malone-Povolny *et al.*, 2019). In addition, arachidonic acid, which is the most prominent fatty acid in snakehead fish, acts as a precursor of prostaglandins and thromboxane, both of which play an active role in the blood clotting process (Palta *et al.*, 2014; Smith *et al.*, 2015).

Transdermal patch technology can be an alternative in DFU treatment (Ramirez-Acuña *et al.*, 2019). The ability to transfer the drugs systemically and locally is a distinct advantage of the patch. In addition, the patch is very convenient for patients, avoids first-pass metabolism of the drug, improves patient compliance, and avoids dose wastage. This method is also very suitable as a replacement therapy for patients who cannot take medicines orally. Therefore, we aim to develop and evaluate the patch for transdermal delivery containing albumin of snakehead fish mucus in wound healing of diabetic rats.

Here, we formulated the transdermal patch containing the snakehead fish mucus albumin in various concentrations. The patch was evaluated for its characteristics and the wound healing activity on diabetic mice.

MATERIALS AND METHODS

Chemicals

The solvents and other chemicals were of analytical grade. Deionized water was obtained through a Millipore-Q50 Ultrapure water system (Sartorius). Alloxan monohydrate and biuret reagent were obtained from Sigma Chemicals Co. (St.

Louis, MO). Vivalbumin® as pure albumin product was obtained from Royal Medicalink Pharmed Co. (Makassar, Indonesia).

Instrumentation

Analytical instrument used a UV-Vis spectrophotometer (LAMDA 365, PerkinElmer Inc. USA). Lyophilization of extract used vacuum freeze dryer (LGJ 10, Armfield Limited, UK). All glassware used were of analytical grade.

Sample preparation

The snakehead fish (*C. striata*) were obtained commercially in Makassar, Indonesia. The fresh snakehead fish were cleaned using clean water and placed in a stainless container. The fish mucus was collected from the skin by evaporation. The corpus was freeze-dried, and then the mucus was steamed at a temperature of 40°C–50°C until forming an extract. The extract was freeze-dried, and the albumin content was measured by UV-Vis spectrophotometry.

Determination of total albumin

The standard curve for determining total albumin content was carried out by preparing biuret reagent in series of 10, 9, 8, 7, 6, 5, 4, 3, 2, and 1 ml. Each of these volumes was added to 10 ml of 2,000 M NH₃. Each mixture was measured on a UV-Vis spectrophotometer at a wavelength of 550 nm. The linearity of the standard series was carried out through analysis. The linearity equation was used to determine the amount of total albumin in the sample. The snakehead fish extract was weighed as much as 1.0 g, and then 50 ml of distilled water was added. The mixture was incubated for 2 hours at 25°C and filtered. As much as 4.0 ml of sample was supplemented with 6 ml of biuret reagent set at 25°C for 30 minutes. The mixture was measured on a UV-Vis spectrophotometer at a wavelength of 550 nm (Fuadi *et al.*, 2017).

Formulation of patch transdermal

According to the previous study, the patch formulation was conducted with slight modification (Chenkuri *et al.*, 2017). The formula can be seen in Table 1. Firstly, the extract of snakehead fish mucus was dissolved in 15 ml of distilled water. The mixture of hydroxypropyl methylcellulose (HPMC) in 8 ml of ethanol, mucilage of sodium carboxymethyl cellulose (Na-CMC), and propylene glycol were added to the sample solution. The mixture was stirred until homogeneous. If there are bubbles during stirring, the preparation must be left to stand for 24 hours to

Table 1. The formula of patch transdermal from the snakehead fish mucus extract.

Materials	Purpose	Formula				
		F(+)	F(-)	F1	F2	F3
Vivalbumin®	Active compound	5%	-	-	-	-
Snakehead fish mucus	Active compound	-	-	1%	3%	5%
Propylene glycol	Plasticizer	5%	5%	5%	5%	5%
HPMC	Polymer	3%	3%	3%	3%	3%
Na-CMC	Polymer	3%	3%	3%	3%	3%
Ethanol 96%	Enhancer	8 ml	8 ml	8 ml	8 ml	8 ml
Distilled water	Vehicle	ad 20 ml	ad 20 ml	ad 20 ml	ad 20 ml	ad 20 ml

remove the bubbles. Furthermore, mold that already contained the formula was put into an oven at a temperature of 40°C for 12 hours (Cherukuri *et al.*, 2017).

- F(+) = Positive control (Formula with Vipalbumin®).
 F(-) = Negative control (Formula without active compound).
 F1 = Formula with snakehead fish mucus extract 1%.
 F2 = Formula with snakehead fish mucus extract 3%.
 F3 = Formula with snakehead fish mucus extract 5%.

Patches' moisture was maintained by placing the patches in a desiccator silica gel at 25°C for 2 × 24 hours. The evaluation of moisture during storage was calculated according to the following equation (Keleb *et al.*, 2010). The desired moisture is less than 10% (Nurmesa *et al.*, 2019).

$$\text{Moisture (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The uniformity of the patch was evaluated by weighing each of the three patches at random, and then the weight variation was recorded. The patch weight requirement is that nothing deviates from 5 to 10% of the average weight.

Animals

The male Wistar rats (*Rattus norvegicus*), weight 200–300 g, were purchased commercially and housed in a cage with food and water availability. The temperature (23°C–25°C) was maintained with a 12 hour light/dark cycle. Rats were grouped into five groups consisting of three rats each: positive control, negative control, treatment by 1%, 3%, and 5% of the extract. Wound observation was carried out for 8 days to see the healing rate of diabetic ulcers in the rats. The study conducted following laboratory guidelines for using animals and was approved by the Health Research Ethics Committee, Universitas Mega Rezky, Makassar, Indonesia, with reference number: 001.C/07.091056/VII/2021.

Alloxan-induced diabetic model

Diabetic rats were prepared following the previous study with light modification. Alloxan monohydrate was weighed and solubilized with 0.2 ml saline individually for each animal according to their weight at a dose of 150 mg/kg body weight. The alloxan was injected intraperitoneally. After 1 hour of alloxan administration, the animals were fed *ad libitum*, and a 5% dextrose solution was given to overcome the hyperglycemic phase. The animals' blood glucose was measured after 48 hour by a glucometer. The diabetic rats (glucose level >300 mg/dl) were separated and divided into five different groups for experimental study, with each group containing three rats (Ighodaro *et al.*, 2017; Kannur *et al.*, 2006).

Wound incision

Rats were exposed to anesthetic doses of ethyl ether by inhalation for 10 min. The back hairs of the rats were shaved, and the skin surface was cleaned with 70% alcohol. The incision (2 cm long and 2 mm deep) was made under aseptic conditions with

surgical blade no. 11 (Arun *et al.*, 2016; Kokan *et al.*, 2009). The normal and diabetic rats were randomly grouped into five groups. The rats in group I was positive control treated by Vipalbumin®; group II was negative control; groups III, IV, and V were treated by the transdermal patch containing snakehead mucus extracts of 1%, 3%, and 5%, respectively.

Wound healing activity

The wound size was measured 2, 4, 6, and 8 days after treatment. The rate of wound healing was measured as the percentage of reduction from the original wound size every single day (Supplementary Figures S1–S5) (Jahandideh *et al.*, 2017). After disinfecting the wound by ethanol 70%, a digital camera was used to take the pictures from an equal distance of the wound and at a right angle to its surface. The wounds were bandaged again after taking the pictures. The percentage of wound healing was calculated using the following equation (Jahandideh *et al.*, 2017):

$$\text{Wound healing (\%)} = \frac{\text{First day wound size} - \text{Daily wound size}}{\text{First day wound size}} \times 100$$

Statistical analysis

All of the present data are mean ± SD of at least three independent experiments. Statistical analysis was performed by GraphPad Prism 8.0 (San Diego, California). Differences between groups were analyzed by one-way analysis of variance, followed by Tukey's multiple comparisons test. The level of statistical significance was set to $p < 0.001$.

RESULTS AND DISCUSSION

Albumin is a protein with a vital function for the body. One of the main functions of albumin is to maintain oncotic pressure so that the supply of nutrients and oxygen is maintained. Hypoalbuminemia is often associated with DM because hyperglycemia is a manifestation of chronic endothelial dysfunction (Dang *et al.*, 2005). Previous studies have found that changes in endothelial function lead to the accumulation of plasma proteins in the interstitial compartment (Plante *et al.*, 1995). This condition causes microalbuminuria, which means reduced blood albumin levels (Basi and Lewis, 2006). Imbalance in blood albumin levels impacts the supply of nutrients and oxygen, which certainly interferes with the wound healing process. Therefore, in this study, we selected diabetic rats as animal models to investigate the effect of albumin-containing patches on wound healing. To compare the wound healing activity of the patch, we applied the patch containing albumin to the normal rats (without DM).

In this study, we used patch containing albumin because we assumed that the topical form would maintain blood albumin levels and initiate wound healing. Previous studies found that albumin promoted NF-κB signaling which, in turn, induced the transduction and transcription of factors involved in wound healing. Albumin infusion plays an essential role in accelerating the wound healing process, as it can contribute to correcting the hypoalbuminemia state (Utariani *et al.*, 2020).

Total albumin of snakehead fish mucus extract

The determination of albumin levels in snakehead fish mucus has never been done, so it is interesting to investigate. Our

study successfully determined the albumin levels in snakehead fish mucus. We found that albumin levels in mucus extracts were much higher than before the extraction process. The comparison of albumin levels in snakehead fish mucus can be seen in Table 2. The albumin content in mucus is closely related to the albumin content in the meat of snakehead fish. Some studies exhibited that snakehead fish contains large amounts of albumin (Baie and Sheikh, 2000; Ramadhanti *et al.*, 2021).

Formulation of patch transdermal

The patch was prepared and characterized as the established procedure. The evaluation was visually carried out, including shape, color, and surface texture. The chemical properties were also evaluated, as shown in Table 3. The organoleptic evaluation showed that the higher the concentration of the active substance used the higher the affect of the shape and color of the patch. Furthermore, all formulas produce good characteristics. The pH measurement by digital pH meter exhibited that the pH of the patch was in the range of tolerated pH for the skin. The requirement for the pH of skin formula to avoid irritation is 4.5–6.5. The pH for all formulas showed acceptable value. Therefore, the formula of the patch is safe for transdermal usage.

Moisture evaluation aims to determine the water content in the patch formula that has been made to protect the active ingredients from microbial growth. The moisture test results showed that all formulas met the humidity requirements listed in Table 3. The humidity requirements for the patch formula should be less than 10%. There is a difference in the percentage of each formula because the concentration of the active ingredients used is different from each other.

The weight uniformity test exhibited that the weights of all formulas were not significantly different from each other, as we can see in Table 4. The difference in weight was due to the amount of active substance used, which affects the weight of each formula. The evaluation of the weight uniformity was conducted to ensure that no significant amounts of weight are lost in the manufacturing process.

Table 2. The albumin level of snakehead fish mucus extract.

Sample	Albumin level (µg/l)	Average (µg/l)
Mucus	3.47	3.47
Extract I	26.48	27.73
Extract II	28.98	

Table 3. Evaluation of patch containing snakehead fish mucus extract.

Formula	Shape	Color	Texture	pH	Moisture (%)
F(+)	Round	Transparent	Smooth	6	2.10
F(-)	Round	Transparent	Smooth	6	1.25
F1	Round	Brown	Smooth	5.9	2.08
F2	Round	Brown	Smooth	5.8	2.36
F3	Round	Brown	Smooth	6	2.40

Wound healing activity

The experimental rats acclimatized were checked for initial blood glucose level, and then alloxan was induced for 3 days. Alloxan works by destroying pancreatic beta cells (Szkudelski, 2001). Alloxan will accumulate in pancreatic beta cells through glucose transport 2 into the cytosol, which will generate reactive oxygen species with a reaction cycle that produces a dialuric acid reaction that will undergo a redox cycle (Song *et al.*, 2015). The redox cycle then forms superoxide radicals which mutate to produce hydrogen peroxide, and the final stage will undergo an iron-catalyzed reaction process to form hydroxyl radical compounds. These hydroxy radicals will damage pancreatic beta cells, resulting in insulin-dependent diabetes mellitus. The use of alloxan as a diabetogenic is also because this drug quickly causes permanent hyperglycemia within 2–3 days (Ighodaro *et al.*, 2017). After 3 days of alloxan administration, the measurement was repeated to compare the initial glucose levels. If rats' blood glucose levels increase over 300 mg/dl, then the rats are considered diabetic (Sikarwar and Patil, 2010).

The percentage of wound healing can be calculated based on comparing the initial wound length and the wound after treatment (Table 5). From the percentage of wound healing of diabetic rats, the most remarkable healing on the sixth and eighth days was seen in the group of patches containing snakehead fish mucus extract 5% (F3 formula). This result was in line with the previous study showing that the greater the concentration of snakehead fish extract given, the greater the wound healing activity of experimental animals (Ramadhanti *et al.*, 2021). 25% cream containing albumin from snakehead fish exhibited that 2% snakehead fish cream for 12 days can accelerate wound recovery (Tungadi *et al.*, 2011). Baie and Sheikh (2000) found that topical albumin treatment could enhance wound healing in the animal experiment by increasing tensile strength and increasing fibroblast count and hydroxyproline level.

Wound healing activity testing on normal rats was carried out to see the difference in wound healing in diabetic rats and normal rats. The data obtained in Table 6 shows a significant difference between the time required for wound healing in normal and diabetic rats. On day 8 for the F3 formula, wounds in normal rats had reached 100% healing, while wounds in diabetic rats had only reached 50% ($p < 0.05$).

The wound healing activity of the patch exhibited that with the length of time the patch was used, the percentage of wound healing in rats increased, as shown in Figure 1. The formula F3 of 58% showed the highest rate on the eighth day. The activity of the positive control group, formula F(+), showed no significant

Table 4. Weight uniformity data of patch containing snakehead fish mucus extract.

Replication	Weight (g)				
	F(+)	F(-)	F1	F2	F3
1	0.08	0.01	0.05	0.13	0.10
2	0.10	0.03	0.06	1.10	0.17
3	0.07	0.02	0.04	0.08	0.10
Average	0.08	0.02	0.05	0.10	0.12

Table 5. The wound healing effect of the patch from the snakehead fish mucus extract toward diabetic rats.

Treatment	Replication	Wound healing (%) at the day			
		2	4	6	8
F(+)	1	7.5	22.5	33	51
	2	3.5	26.5	38.5	52.5
	3	5	15.5	32	54
F(-)	1	1	11	22.5	45
	2	0.5	14	28	44.5
	3	1.5	15.5	20.5	29
F1	1	2.5	18.5	30	35
	2	6.5	23	35	40
	3	2.5	23.5	32.5	43.5
F2	1	19.5	28	33.5	50.5
	2	3.5	29.5	39.5	56.6
	3	5.5	33.5	38.5	56
F3	1	3.5	29	44.5	55.5
	2	8.5	29	48.5	59.5
	3	4.5	18.5	44.5	59

Table 6. The wound healing effect of the patch from the snakehead fish mucus extract toward normal rats.

Treatment	Replication	Wound healing (%) at the day			
		2	4	6	8
F(+)	1	0	35	90	100
	2	0	40	90	100
	3	5	40	85	100
F(-)	1	0	15	35	70
	2	0	5	35	65
	3	0	10	25	80
F1	1	0	10	55	80
	2	0	10	65	85
	3	0	5	55	75
F2	1	0	10	65	90
	2	0	25	70	95
	3	0	25	70	95
F3	1	0	65	80	95
	2	0	30	70	100
	3	5	75	95	100

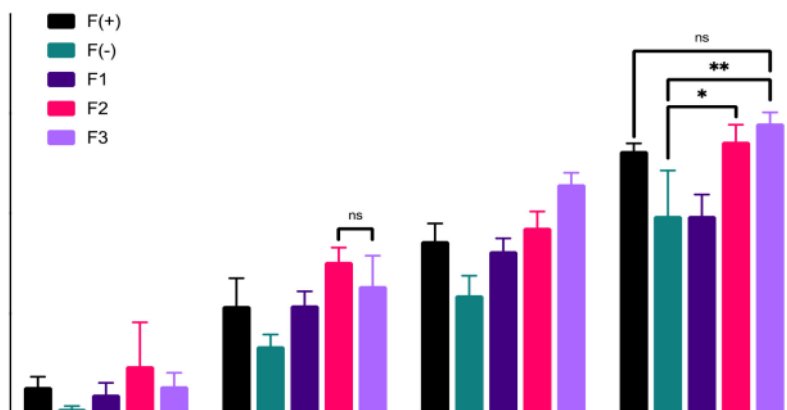


Fig 36. Wound healing activity of patch containing snakehead fish mucus extract. No significant (ns), $p < 0.05$ (*), $p < 0.001$ (**).

difference from the action of formula F3 on the eighth day of treatment. These data indicate that the wound healing ability of formula F3 is the same as that of formula F(+). On the contrary, formula F3 and F2's wound healing activity differed significantly from the negative control formula F(-) with $p > 0.001$ and $p > 0.05$, respectively.

Although wound healing is a natural physiological response to tissue wounds, it is a complex phenomenon and involves a complex interplay between multiple cell types, mediators, cytokines, and the vascular system. The healing process starts from vasoconstriction of blood vessels and platelet aggregation to stop bleeding. After that, the inflammatory cells come to release various mediators and cytokines to stimulate angiogenesis, thrombosis, and re-epithelialization (Ozgok Kangal and Regan, 2021). The characteristics of rats on the first day after treatment showed wound enlargement due to the inflammatory phase. On the third and fifth days, the wound healing phase proliferation is characterized by the formation of granulation tissue in the wound, collagen formation, and fibroblasts (Ansar and Ghosh, 2016). The next phase is the maturation phase consisting of re-absorption of excess tissue, shrinkage due to gravity, and forming new tissue. The healing phase ended when all signs of inflammation had disappeared, as shown on observations on the seventh day to the ninth day, where all the wounds in the mice had healed (Ansar and Ghosh, 2016; Utami *et al.*, 2020).

Albumin plays a vital role in wound healing in this study because albumin can activate epidermal growth factor receptor (EGFR) expression and upregulate NF- κ B signaling. By the activation of EGFR could accelerate corneal epithelialization. In addition, the EGFR stimulates tyrosine kinase activity that activates gene transcriptions, DNA synthesis, and cell proliferation (Fawwaz *et al.*, 2020; Shu *et al.*, 2019).

High essential amino acid components and fatty acids in snakehead fish albumin play a major role in wound healing (Haniffa *et al.*, 2014; Zuraini *et al.*, 2006). Both of these components work through the initiation of collagen synthesis and re-epithelialization. Other studies say that Arginine is an amino acid substance that plays an important role in healing (Anar *et al.*, 2014). The polyunsaturated fatty acids (PUFA) also play a role in the immune response in wound healing. PUFA works as a

substrate of prostaglandin, thromboxane, leukotrienes, and lipoxin synthesis (Guo and DiPietro, 2010). The deficiency of these components will slow down the healing process (Jais *et al.*, 1994).

CONCLUSION

The patch transdermal from the snakehead fish mucus extract was formulated with the acceptable characteristics. The formula F3 with 5% extract showed the best activity toward wound healing of diabetic rats on the eighth day of treatment. Therefore, the formulation of patch transdermal containing snakehead fish mucus extract 5% can accelerate wound recovery. However, further research is needed to support the current data.

ACKNOWLEDGMENT

This work was supported by Universitas Megarezky and Universitas Hasanuddin, Makassar, South Sulawesi, Indonesia. Special thanks to the Future of Science Research Group for providing statistical analysis software GraphPad Prism 8.0.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

The institutional animal ethics committee approved the study protocol at Health Research Ethics Committee, Universitas Mega Rezky, Makassar, Indonesia, with reference number: 001.C/07.091056/VII/2021.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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PUBLISHER'S NOTE

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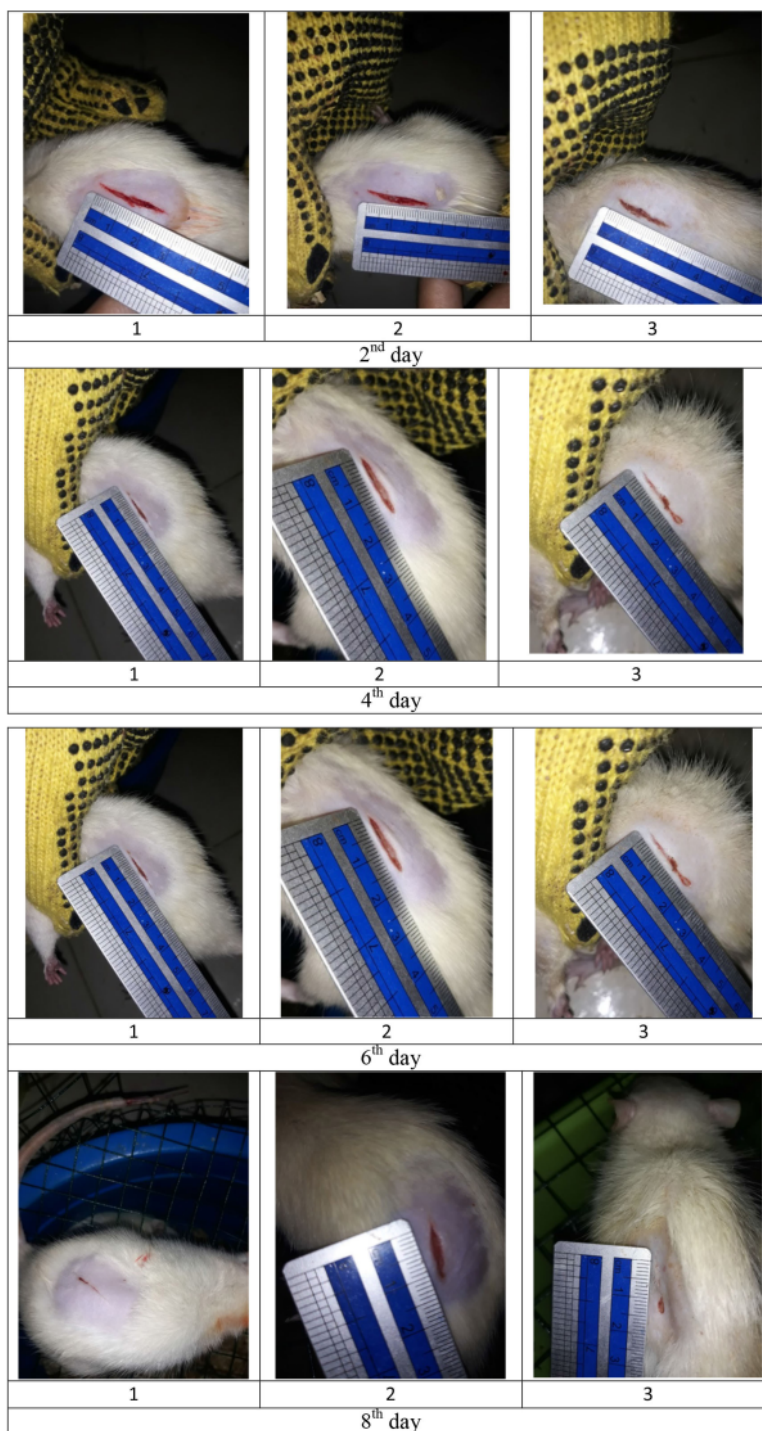


Figure S1. Wound size of diabetic rats as negative control F(-).

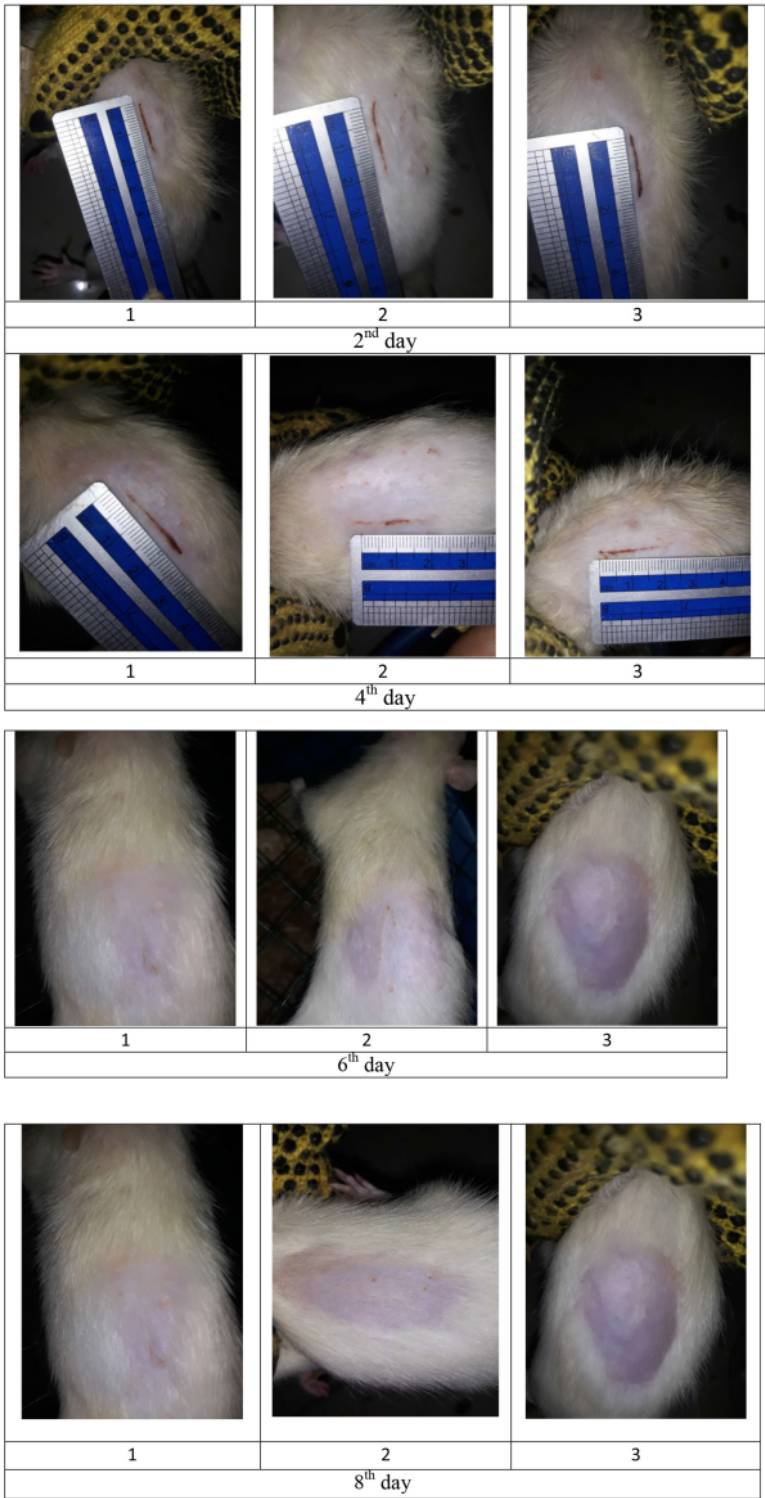


Figure S2. Wound size of diabetic rats as positive control F(+).

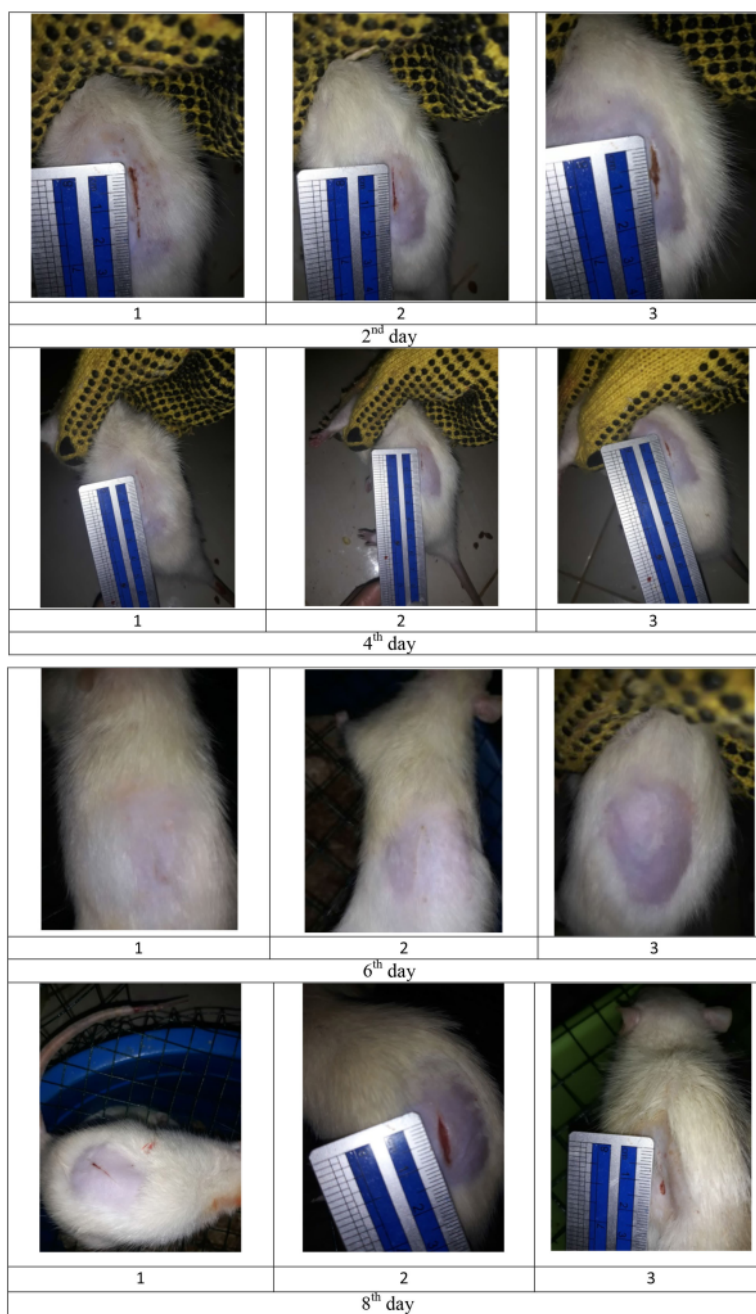


Figure S3. Wound size of diabetic rats as treatment F1.

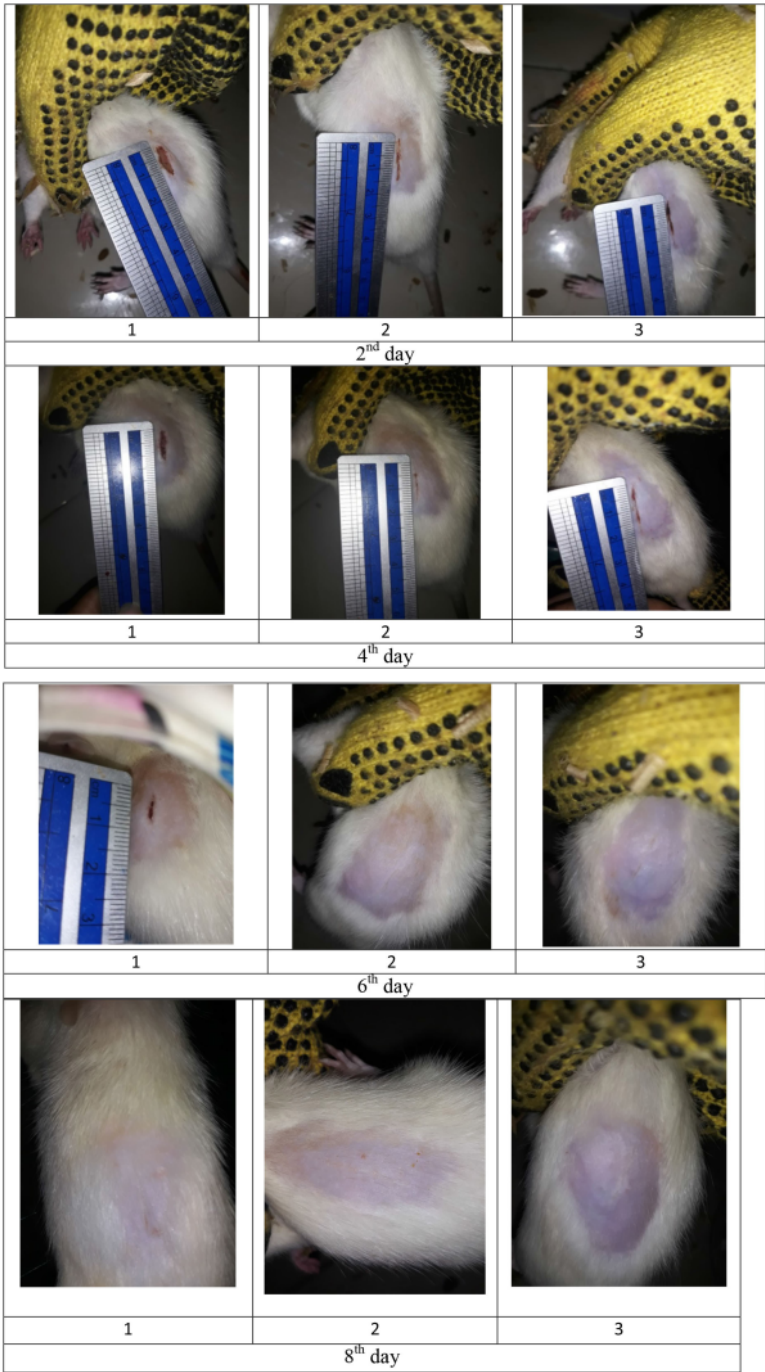


Figure S4. Wound size of diabetic rats as treatment F2.

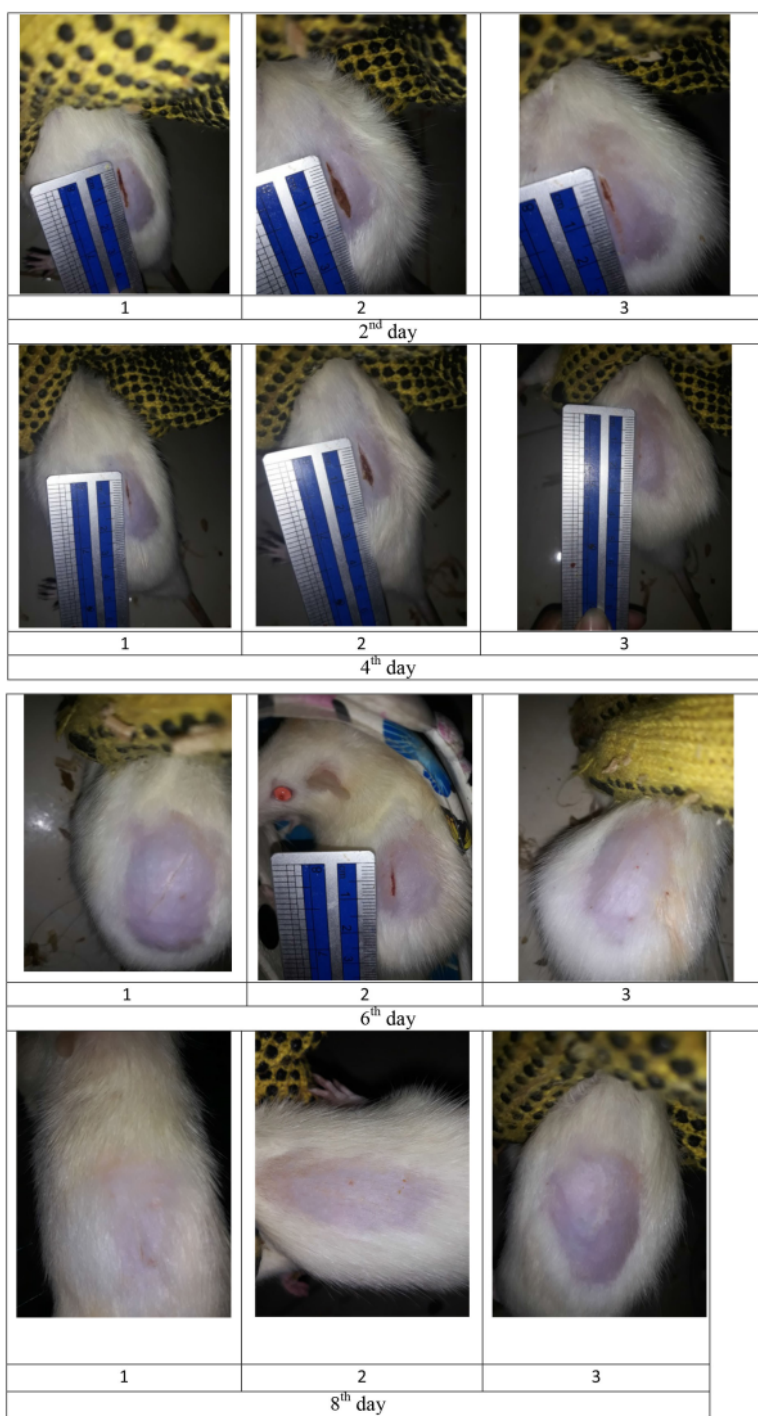


Figure S5. Wound size of diabetic rats as treatment F3.

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