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Nanoemulgel Activity of Binahong Leaf Extract (*Anredera cordifolia* (Ten.) Steenis) againts Wound Healing of Hyperglycemic Rats

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ABSTRACT

Hyperglycemia is a condition where blood sugar levels exceed normal limits. This is related to damage throughout the body, causing ulcers on the legs or so-called diabetic wounds. The content of flavonoid compounds, steroids and saponins in binahong leaves plays a role in healing diabetic wounds. This study aims to determine the wound healing activity of diabetes in nanoemulgel preparations of binahong leaf extract (*Anredera cordifolia* (Ten.) Steenis) with its extract in male rats wistar hyperglycemia. The study group was divided into 4 groups got each negative control group, positive control group, N1 test group, and N2 test group. Measurements of the diameter of diabetic wounds is carried out on days 1, 5, 14 and 16. On the 16st day or as one of the groups healed, animals were sacrificed to continue histopathological testing of wound tissue with Hematoxylin-Eosine staining and saw an increase in the number of fibroblasts and thickening of the epithelium. Diabetic wound healing results between the positive control group and the N1 treatment showed significant differences compared to the negative controls versus N2 treatment of diabetic wounds healing. The results of histological observations showed thickening of the epithelium and increase in the number of fibroblasts of the positive control group and significantly different N1 treatments to negative controls versus N2 treatment. Nanoemulgel is accelerating the healing process of rat diabetic wounds, as well as accelerating the reepitalization process by increasing the thickness of the epithelium and fibroblast tissue compared to the binahong leaf extract group.

Keywords: *Anredera cordifolia* (Ten). Steenis, Activity, Diabetic Wounds, Nanoemulgels.

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INTRODUCTION

Hyperglycemia or high blood sugar levels are conditions when the level of sugar in the blood exceeds normal limits. This can be caused by insulin deficiency due to beta cell damage and or insulin resistance in the liver and muscles (Apriani et al., 2011). Hyperglycemia is associated with damage to some organs, such as narrowing of blood vessels, hardening of blood vessels as well as nerve damage throughout the body. This causes ulcers on the legs or called diabetic wounds. In general, the treatment of diabetic wounds in the community is carried out with a bandage accompanied by betadine compresses and normal saline. However, the long-term use of the dressing can lead to slow wound healing and can appear various infections (Mutiara et al., 2015).

The wound healing process involves several processes including the inflammatory, proliferation, maturation and remodeling phases involving various cells such as fibroblast cells that are responsible for the formation and maintenance of connective tissues produced by macrophages in the inflammatory phase which play an important role in repairing tissues. Fibroblast cells are the most common cells found in the connective tissue layer. In the proliferation phase, there is an increase in the number of wound components, one of which occurs fibroblast proliferation.

One of the plants associated with improving the condition of diabetes mellitus through a decrease in blood glucose level and healing diabetes wounds that has been widely used in Indonesia is the binahong plant (Anredera cordifolia (Ten.) Steenis). Binahong contains the main compounds flavonoids, saponins, steroids/terpenoids that work in lowering blood sugar, accelerating wound healing through increased number of fibroblast cells and thickening of the epithelium (Hu et al., 2014; Mutiara et al., 2015; Patra, 2012). However, treatment using natural ingredients has a drawback, namely the relatively small content of active substances so that large doses are needed, which can cause the administration of drugs not acceptable.

One of the uses of herbs developed in pharmaceutical preparations is through nanoemulgel. Nanoemulgel is an emulsion preparation with a droplet size of 1-100 nm suspended in a hydrogel. Oil components, surfactants and cosurfactants can increase the penetration of active substances so that it will increase therapeutic activity. Based on research conducted by (Anwar et al., 2021), obtained the optimal formula of nanoemulgel binahong leaf extract (Anredera cordifolia (Ten.) Steenis) with formulas and formulations that support the transdermal activity of the drug, but the wound healing activity of the preparation is not yet known. The purpose of this study was to determine the activity and mechanism of wound healing of diabetic nanoemulgel binahong leaf extract (Anredera cordifolia (ten.) Steenis) in Wistar male rats.

MATERIALS AND METHOD

Materials

Fresh binahong leaves come from the Allizzu herbal garden, Bantul district, Yogyakarta, aquadest, carbopol 940, chloroform, disposable, ethanol 96%, formalin 10%, glucose, hypafix, iodine 5%, ketamine hydrochloride, madecassol 1%, methylparaben, oral dispo, PEG 400, propylene glycol, standard rat feed, triethanolamine (TEA), tween 80, VCO.

Methods

Nanoemulgel Making

The EDB nanoemulgel formula to be tested for activity can be seen in Table I.

Table I. BLE nanoemulgel formula

No	Materials	Consentration (%)
1	Binahong leaf extract	5
2	Tween 80	50
3	PEG 400	26,25
4	VCO	6,25
5	Aquadest	12,5
6	Nanoemulsions	25
7	Carbopol 940	2,5
8	TEA	2
9	Metilparaben	0,05
10	Propilenglikol	10
11	Aquadest	60,45

The manufacture of nanoemulgel begin with mixing tween 80 and PEG 400 as a mixture of 1. Mixture 1 is added into the oil phase and stirred using a magnetic stirrer for 2 hours and recorded as mixture 2. The binahong extract is dissolved into the aqueous and put into the mixture 2 little by little while stirring using a magnetic stirrer hotplate for 1 hour. The mixture was further sonicated for 1 h until a nanoemulsion formed (Sanaji & Liananda3, 2019). The nanoemulsions that have been made are then tested for percent transmitter to determine the clarity of the nanoemulsions formed as an illustration of the formation of nanometer-sized droplets.

The addition of a gel base is carried out by first developing Carbopol 940 in hot aqueous for 24 hours. The expanded carbopol is added with TEA little by little until a gel mass is formed. Methyl parabens are dissolved in propyllenglikol and added to the already formed gel base. The nanoemulsions are then added into the gel base little by little and homogenized using a mixer until a mass of nanoemulgel is formed (Handayani et al.,, 2015). Nanoemulgel preparations are then characterized as including organoleptic, dispersal, adhesion, pH and viscosity (*viscometer* Rheosys Merlin VR).

Diabetic Wound Healing Activity Test

The number of experimental animals used is based on the calculation of the freed formula, namely (n-1) (t-1) ≥ 15, where t is the number of groups, while n is the number of test animals of each group of groups. The test animals used in this study were white rats (Rattus norvegicus) as many as 24 male sex that weighed 150-250 g which were divided into 4 groups, namely:

a. Negative control group (glucose + nanoemulgel base)
b. Positive control group (glucose + madecassol 1%)
c. N1 treatment group (glucose + EDB nanoemulgel preparation)
d. N2 treatment group (glucose + binahong leaf extract)

The test animals were adapted in a new environment for 7 days before testing, then satisfied first 12 hours before being given glucose and checked blood sugar levels using a glucometer. Glucose administration is carried out orally at a dose of 4.5 g / KgBB for 8 days. Glucose is dissolved with 3 mL of aquaades and made in fresh condition for use within 10-15 minutes. Checking the blood sugar level (KGD) of the test animal is carried out after glucose administration (Tanuwijaya et al., 2019).

Hyperglycemia wound creation if blood sugar levels ≥135 mg/dL (Wolfensohn, 2013). Previously, rat hair was shaved to the back marked with a size of 3x5 cm. Test animals were anesthetized first using ketamine hydrochloride 0.1 mL at a dose of 3-5 mg/KgBB intramuscularly.

The test animal was put in a cage and waited for 5 minutes until the test animal lost consciousness. The back of the test animal was then disinfected using 5% iodine povidon in the area to be injured. The back was wound using a 5 mm biopsy punch with a depth of 1 mm using scalpel handle no.3 and surgical blade no.10.

Topical application of EDB nanoemulgel preparations in rat wounds was carried out 2x every 12 hours for 16 days (Tanuwijaya et al., 2019). The measurement of the wound diameter begins on the first day the rat is excised, measured using a calipers on four sides of the wound diameter so that a percentage of wound closure is obtained. Observation of diabetic wound healing is carried out on the 1st, 5th, 14th and 16th days. Calculation of the percentage of wound closure is calculated using formula 1.

$$\%PL = \frac{d_0 - d_n}{d_0} \times 100\% \quad \text{.....(1)}$$

Description : d_0 = initial wound diameter
d_n = wound diameter on the day of observation

Histopathological Testing

On the 16th day the test animal was sacrificed to continue histopathological testing of wound tissue. Skin tissue is taken a made histopathological preparations with Hematoxylin-Eosin staining according to standards carried out at the Pathology Laboratory of the Faculty of Medicine UGM, Yogyakarta. The slides that have been created were observed with a light microscope magnified 400 times and saw an increase in the number of fibroblasts and the thickness of the epithelium.

Data Analysis

Data on wound closure diameter, increase in fibroblast count and epithelial thickening were each statistically analyzed using the SPSS 16.0 program with the Shapiro-Wilk test, followed by the Kruskal-Wallis test. The statistical test is continued with Mann-Whitney if the value is asymp. Sig. <0.05 Signification is established if p<0.05.

RESULT AND DISCUSSION

Diabetic Wound Making

Hyperglycemia rats were then anesthetized using ketamine hydrochloride at a dose of 125 mg/KgBB intramuscularly. The wound is made using a 5 mm biopsy punch with a depth of 1 mm at the moment when the rat loses consciousness at the 10-15th minute.

Administration of Nanoemulgel BLE to Cover Diabetic Wounds

Topical application of BLE nanoemulgel preparations is carried out every 2 times a day on the 1st to the 16th day. Observations on diabetic wound closure obtained data as in Table II.

Table II. Mean diameter of ± SD wounds of rats at various treatments and times

Group	Diabetic wound healing (mm)			
	Day-1st	Day-5th	Day-14th	Day-16th
Negative Control	4,5 ± 0	4,28 ± 0,06	2,49 ± 0,54	2,1 ± 0,27
Positive Control	4,5 ± 0	3,6 ± 0,28*	1,25 ± 0,68*	0*
N1 Treatment	4,5 ± 0	3,7 ± 0,31*	0,76 ± 0,36*	0*
N2 Treatment	4,5 ± 0	4,24 ± 0,07	2,42 ± 1,50	1,7 ± 1,32

* = significantly different (p<0.05) compared to negative control group

Based on the data obtained in Table II, the diabetic wounds of the positive control group and the N1 treatment group experienced a faster closure compared to the negative control group. On the 1st day all groups did not show any wound healing. Significantly different wound healing ($p<0.05$) was demonstrated by the positive control group and the N1 treatment on the 5th, 14th, and 16th days compared to the negative control group. In contrast to the N2 treatment group showed no significantly different wound closure ($p>0.05$) compared to negative controls on days 5, 14th and 16th. A graph of the diabetic wound closure of rat hyperglycemia of each group can be seen in Figure 1.

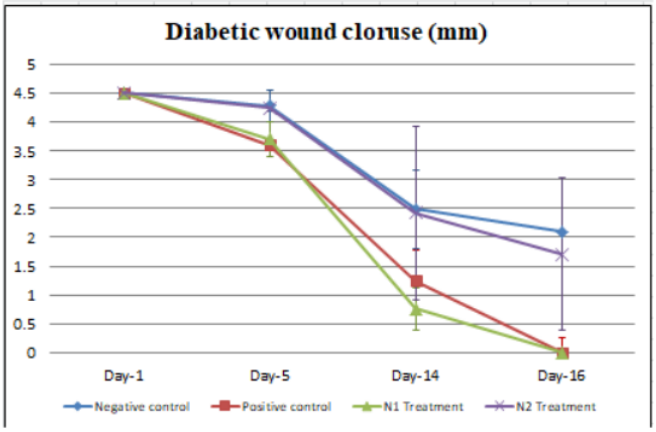

Fig 1. Graph of diabetic wound closure in hyperglycemia rats at various treatments and times
Description: negative control, (nanoemulgel base), positive control (madecassol 1%), N1 treatment (Nanoemulgel EDB), and N2 treatment (binahong leaf extract), (Day 1 begins when rats are in a state of hyperglycemia of all groups, namely day 8 after being given glucose orally)

The closure of this diabetic wound proves that the secondary metabolite compounds in the extract are flavonoids that act as anti-inflammatory through inhibitory effects on the arcachidonic acid metabolism pathway, the formation of prostaglandins, and the release of histamine in inflammations, as antimicrobials and accelerate the work of neutrophils in fighting bacterial infections (Landen et al., 2016; Wang et al., 2016), Antioxidant (Munhoz et al., 2014), Saponin compounds are antiseptic and influential in spurring the proliferation of fibroblasts and the formation of collagen which plays a role in healing diabetic wounds (Melguizo et al., 2021; Sukandar et al., 2011), Polyphenol compounds act as antimicrobials by disrupting the constituent components of peptidoglycan in bacterial cells that cause cell death. Dead cells will be phagocytized by macrophages, accelerating the wound healing phase (PI et al., 2015). In addition, it can accelerate wound healing through increased excretion of TGF-β and PDGF genes (Melguizo et al., 2021; Sutrisno et al., 2016).

Wound closure in the N1 treatment group was faster compared to the N2 treatment group. This is because binahong leaf extract formulated in the form of nanoemulgel will more easily penetrate the membrane. The active substances in binahong leaf extract are difficult to penetrate the lipid membrane because it has a larger molecular size and low solubility in water so that the absorption of binahong leaf extract becomes low (Hanutami, 2020). When compared to research (Kintoko, 2015), which formulates binahong leaf extract in gel form requires a higher concentration of extract to be able to provide a diabetic wound healing effect of 30% (Rahman, 2018).

Histopathological Observations of Wounds

Histopalogic observation of the wound is aimed at knowing the changes occurring in the skin tissue microscopically. In this study, reepitalization and an increase in the number of fibroblasts with HE staining were seen. The wound healing process is greatly influenced by the reepitalization process in the proliferation phase, the faster the reepitalization process, the faster the wound closure will be so as to accelerate wound healing. The epitalization process involves various proteins and several factors. Fibroblast cells function in the formation of connective tissue. Fibroblasts can produce collagen, reticulum, elastin, glycosaminoglycans, glycoproteins and protein matrices that serve to repair tissues.

The results of testing using a microscope can be seen in Figures 2 and 3. As well as the average epithelial thickening and fibroblast scoring can be seen in Tables III and IV.

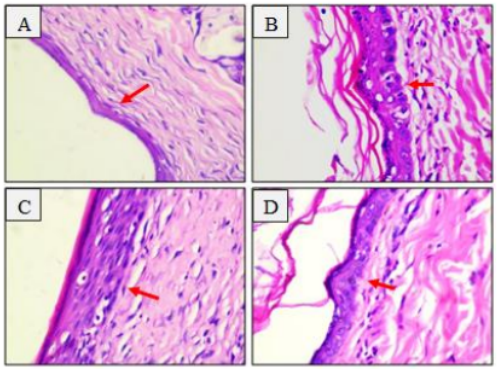

Figure 2. Epithelial thickening with HE staining using Olympus Microservice microscop with 400x magnification

Description: A: negative control (nanoemulgel base), B: positive control (madecassol 1%), C: N1 treatment (binahong leaf extract nanoemulgel), and D: N2 treatment (binahong leaf extract), (arrows indicate epithelial thickness on the skin tissue of the test animal each kalompok)

Table III. Average epithelial thickening of each group after treatment for 16 days

Group	Epithelial thickness (μm ± SD)
Negative Control	33,52 ± 9,86
Positive Control	109,69 ± 45,13*
N1 Treatment	89,44 ± 10,36*
N2 Treatment	49,31 ± 16,14

* = significantly different ($p<0.05$) compared to negative control group

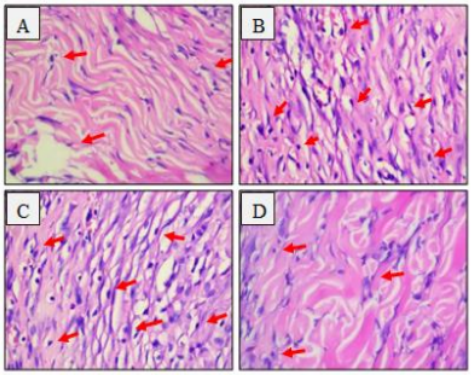

Figure 3. Increased number of fibroblasts (arrows) with HE staining using Olympus Microservice microscop with 400x magnification

Description A: negative control (nanoemulgel base), B: positive control (madecassol 1%), C: N1 treatment (binahong leaf extract nanoemulgel), and D: N2 treatment (binahong leaf extract), (arrows indicate fibroblasts on the skin tissue of the test animal each group)

Table IV. Scoring the average number of fibroblasts of each group after treatment for 16 days

Group	Number of fibroblasts (Score ± SD)
Negative Control	10,66 ± 9,64
Positive Control	32 ± 34,42*
N1 Treatment	32,77 ± 33,40*
N2 Treatment	14,55 ± 14,67

* = significantly different ($p<0.05$) compared to negative control group

Based on the results of histopathological observations of epithelial thickening and fibroblast cell enhancement, diabetic wounds in the positive control group and N1 treatment showed a significantly thicker epithelial layer ($p<0.05$) compared to the negative control group. Meanwhile, diabetic wounds in the N2 treatment group showed a thick epithelial layer that did not differ significantly ($p>0.05$) compared to the negative control group. Likewise with the increase in the number of fibroblast cells, where the negative control group and the N1 treatment showed a significantly different increase in the number of fibroblasts ($p<0.05$) compared to the negative control group. Whereas the N1 treatment group showed a significantly different number of fibroblast cells ($p>0.05$) compared to the negative control group. This is due to the presence of active compounds of binahong leaf ethanol extract including flavonoids that act as anti-inflammatories that can stimulate the proliferation of fibroblasts, support the epithelialization process, the formation of prostaglandins, and the release of histamine in inflammations so as to accelerate the wound healing phase (Mutiara et al., 2015). The content of saponins and terpenoids can spur the proliferation of fibroblasts and collagen formation and accelerate the epithelialization of wounds that play a role in healing diabetic wounds (Patra, 2012; Sukandar et al., 2011). In addition, it is influenced by binahong leaf extract formulated in the form of nanoemuglel. Nanoemulgel easily penetrates the membrane so that it helps the permeability of drugs on the surface of the membrane because the skin membrane is lipophilic, and can maintain the oxidative stability of antioxidant compounds by accumulating oxygen molecules in the oil-water interphase (Rahman, 2018).

CONCLUSION

Based on the research conducted, it was concluded that the administration of nanoemulgel preparations of binahong leaf extract is more effective in accelerating the healing of diabetic wounds in hyperglycemia rats compared to binahong leaf extract. The wound healing mechanism of hyperglycemia rats given nanoemulgel preparations of binahong leaf extract through an epithelialization process with an increase in epithelial thickness and fibroblast cell count when compared to binahong leaf extract.

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