*Pharmaceutical Nanotechnology*, 2021, *9*, 339-346

RESEARCH ARTICLE

# The Potency of Wound Healing of Nanogel-containing *Mikania micrantha* Leaves Extract in Hyperglycemic Rats

Imam B. Sumantri[1,*], Ismayadi [2] and Lolyta F. Mustanti[3]

[1]*Department of Biology, Faculty of Pharmacy, University of Sumatera Utara, Medan-20155, Indonesia;* [2]*Department of Community Nursing, Faculty of Nursing, University of Sumatera Utara, Medan-20155, Indonesia;* [3]*Faculty of Pharmacy, University of Sumatera Utara, Medan-20155, Indonesia*

**Abstract:** ***Introduction*:** *Mikania micrantha* has been traditionally used for wound dressings and to promote the healing of sores. This is due to the content of alkaloids and terpenoids/steroids compounds. Hyperglycemia is a good medium for bacterial growth that inhibits the wound healing process.

***Purpose*:** This study aimed to determine the wound healing of nanogels containing MMLE in hyperglycemic rats as a model for diabetic wounds.

***Methods*:** *Mikania micrantha* leaves were extracted with the maceration method using 96% ethanol in 5 days. Carbopol 940 was used as the gelling agent. The parameters observed during the physical testing of nanogels were organoleptic, homogeneity, pH, and size of the particle. Antibacterial activity was tested on *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Escherichia coli*. Moreover, wound healing activity was tested in hyperglycemic rats after observing for 14 days. Diabetic wound healing was treated with 4 groups (P1, P2, K1, K2). Data were analyzed using SPSS.

***Results*:** Nanogel showed homogeneity, dark green color, transparency, pH 6.1± 0.1, and particle size range in 255-456 nm. The inhibition zones of antibacterial testing, *i.e.*, *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Escherichia coli*, were 10.57 ± 0.26 mm, 9.73 ± 0.21 mm, and 8.4 ± 0.1 mm. The percentage of diabetic wound healing was in the range of 92.79±3.81% to 94.08 ± 2.33% for 14 days of observation.

***Conclusion*:** MMLE nanogels have the potential as a treatment for diabetic wound healing.

ARTICLE HISTORY

Received: August 31, 2021
Revised: October 08, 2021
Accepted: November 06, 2021

*DOI:*
*10.2174/2211738509666211209164105*



**Keywords:** Antibacterial, hyperglycemic rats, formulation, *Mikania micrantha*, nanogel, wound healing.

## 1. INTRODUCTION

Diabetes is a chronic metabolic disease with a prevalence of about 463 million (20-79 years) or equal to 9.3% of the world's population in 2019. Indonesia is in 7 out of 10 countries with the highest sufferers of diabetes, with a prevalence of around 11.3% of the Indonesian population [1]. Uncontrolled blood sugar levels increase the level of fatty substances in the blood (atherosclerosis). Poor blood circulation to the extremities can cause ulcers. High blood sugar is a good medium for bacterial growth, so diabetic ulcer patients are very often infected [2]. In addition, complications resulting from diabetes mellitus (DM) include ischemia, and this condition inhibits the wound healing process [3]. Around 8.7% of diabetic patients in Indonesia experience diabetic foot ulcers, and 1.3% are amputated. Diabetic foot ulcers are one of the most common chronic complications characterized by injury and inflammation in the area under the ankle. Therefore, diabetic wound management is very important to avoid damage that leads to amputation [4]. Wound management and the efficacy of wound healing in an occlusion of the injured tissue can highly depend on the material used in the wound dressing [5]. Wound management is usually carried out on diabetic foot ulcers that are a debridement, maintaining wound moisture, controlling the inflammation and the infection. One of the most common attempts is to control the inflammation and the infection by using topical antibacterial [6].

*Mikania micrantha* is an Asteraceae family known as sembung rambat. *Mikania micrantha* leaves contain alkaloids, terpenoids, and steroids [7]. Traditional therapy has been shown to reduce inflammation and accelerate wound healing [8-10]. *Mikania micrantha* leaves are commonly used in traditional medicines foranalgesia, skin bleeding, healing sores, antimicrobials, skin infection, and ulcers [7, 11]. Nanotechnology has demonstrated the potential to increase the absorption of the active substance and the action

* Address correspondence to this author at the Department of Biology, Faculty of Pharmacy, University of Sumatera Utara, Medan-20155, Indonesia; Tel: +62821-6377-9029; E-mail: imambagus@usu.ac.id

 

potential of the drug, promote the sustained release of the active substance, reduce the dose required, and increase biological activity [12, 13]. Nanogels are mostly used in nanomedical applications as novel drug carriers for response-based therapy [14].

It is, therefore, necessary to perform further research to evaluate nanogels of *Mikania micrantha* leaves extract on the wound healing in rats under hyperglycemic conditions and the antimicrobial activity.

## 2. MATERIALS AND METHODS

### 2.1. Plant Materials

*Mikania micrantha* leaves were collected from Deli Serdang District, North Sumatera. The plant was identified by Herbarium Medanese, University of Sumatera Utara.

### 2.2. Preparation of Standardized *Mikania micrantha* Leaves Extract (MMLE)

#### *2.2.1. Extraction*

*Mikania micrantha* leaves were dried at room temperature and smashed manually. Simplicia was extracted by the maceration method with ethanol 96% at room temperature for 5 x 24 h. The liquid extract obtained was then evaporated with a rotary evaporator. Crude extracts were packaged in dark bottles, stored in a refrigerator at 4C, and then used.

### 2.3. Phytochemical Screening and Physicochemical Analysis

Simplicia and extracts were subjected to phytochemical screening by identification using different spraying reagents for particular compounds, such as dragendorf for alkaloids, $AlCl_3$ for flavonoid, $FeCl_3$ for tannin, Lieberman Burchard for steroids, and sulfuric acid for saponins/triterpenoids. Analysis of extracts physicochemical was carried out for properties, such as water and ethanol-soluble extract, water content, total ash content, and acid-insoluble ash content according to Farmakope Herbal Indonesia.

### 2.4. Preparation of Nanogels and Gels Containing MMLE

The nanogel containing MMLE was prepared with the formulations shown in Table **1**. The nanodispersions of the MMLE were prepared by the modified emulsification-diffusion method. MMLE were added in Tween 80, then dissolved in sorbitol. This phase was mixed with constant stirring at 5,000-10,000 rpm using a high-speed homogenizer. The dispersion resulting from MMLE was converted into nanodroplets. The gel phase was prepared by dispersing a gel-forming agent carbopol 940 in hot water containing nipagin and nipasol. Nanodispersions of gel were prepared by dispersing the gel phase in the nanodroplet by using a high--speed stirrer. The pH was adjusted by using triethanolamine to form the nanogels. Nanogels containing MMLE were stored at room temperature [15, 16]. Gels of MMLE were prepared by the same formulation of nanogels, without Tween 80 and procedures without going through a high stirrer process.

**Table 1. Formulation of Nanogel Containing MMLE.**

| Ingredients | Composition |
|---|---|
| MMLE | 2% |
| Carbopol 940 | 1% |
| Tween 80 | 16% |
| Sorbitol | 14% |
| Nipagin | 0.1% |
| Nipasol | 0.02% |
| Triethanolamine | 1% |
| Aquadest | Ad 100% |

### 2.5. Physical Examination of Nanogels Containing MMLE

The parameters observed during the physical testing of nanogels were organoleptic, homogeneity, pH, and size of particles. Organoleptic was inspected visually for their color and aroma. The pH was measured at room temperature using a digital pH meter which was calibrated before each use with a standard buffer solution [5]. The mean size and polydispersity index of the size distribution of the selected nanogels were determined by using Vasco CORDOUAN Technologies Particle Size Analyzer. The mean particle size and size distribution were recorded.

### 2.6. Antibacterial Activity

Three bacterial pathogens, *i.e.*, *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Escherichia coli* were used in this study. The treatment group was divided into gels (P1) and nanogels (P2) containing 2% of MMLE. Treatment groups were impregnated with inoculated agar nutrient medium to study the antibacterial activities. The inoculation of bacterial cultures was incubated overnight at 28˚C for 24 hr. Well diffusion method [17] for assessing the antibacterial activity was applied using Muller Hinton agar medium. After the incubation period, the diameter of the inhibition zones was measured [18].

### 2.7. *In Vivo* Diabetic Wound Healing Study

#### *2.7.1. Animal Group*

This research was conducted with permission from the Animal Research Ethics Committee, University of Sumatera Utara No. 0226/KEPH-FMIPA/2019. Twenty-four Wistar rats aged 3-4 months old were used, with body weights of 155 ± 10 g. They were divided into 4 groups. The treatment group of *In vivo* diabetic wound healing study is shown in Table **2**.

### 2.8. Induction of Diabetic

Diabetes test animals were induced with alloxan at the dose of 120mg/kg body weight. Examination of fasting blood glucose levels was carried out before treatment on

days 1 and 10 of topical application of test preparations according to the treatment group. Blood glucose status by the glucometer and only animals with blood glucose greater than 200mg/dL were included in the study [19].

**Table 2. The treatment group of diabetic wound healing study.**

| Group | Remarks |
|---|---|
| P1 | Diabetic experimental rats treated with MMEL gels |
| P2 | Diabetic experimental rats treated with MMEL nanogels |
| K1 | Diabetic experimental rats treated with MMEL cutimed® gel |
| K2 | Diabetic experimental rats treated with gel base |

### 2.9. Wound Excision

All rats were anesthetized with an intraperitoneal injection of ketamine at dose 2mg/kg body weight. The backsides of the right and left of each rat were shaved and outlined for the area of the wound with a marker. Excision was created with an area of approximately 4cm$^2$ using a sterile surgical scissor and considered as day zero [20].

### 2.10. Sample Treatment

The wounds were treated with topical application of each group treatment every day for 14 days. On days 1, 3, 5, 7, and 14 post excision, the wounds areas were measured for all rats. The percentage of wound healing is calculated as follows [21, 22]:

$$Wound\ healing\ (\%) = \frac{wound\ area\ on\ day\ (zero)\ - wound\ area\ in\ day\ (n)}{wound\ area\ on\ day\ (zero)} \times 100\%$$

### 2.11. Statistical Analysis

Data were analyzed using IBM SPSS Statistics 22 software. Results were presented as mean ± standard deviation. Statistical significance was assessed with Kruskal Wallis, and the Mann-Whitney U. Kruskal-Wallis test was used to compare the mean of all groups. Mann-Whitney test was used for intergroup comparison.

## 3. RESULTS

### 3.1. Standardized MMLE

Maceration was conducted to obtain the chemical components in *Simplicia*. The yield of concentrated extract was 37.12% of dark green color with a typical scent. The physicochemical analysis is responsible for ensuring the quality and purity of *Simplicia* and extract of *Mikania micrantha*. The result of physicochemical analysis of *Simplicia* such as water and ethanol-soluble extract, water content, total ash content, and acid-insoluble ash content is shown in Table **3**. Further, the result of physicochemical analysis of Simplicia, such as water content, total ash content, and acid-insoluble ash content, is shown in Table **4**. The phytochemical screening showed *Simplicia* and extract of *Mikania micrantha* leaves, as depicted in Table **5**. Both *Simplicia* and extract contained the same phytochemical constituents.

**Table 3. Physiochemical analysis of *Mikania micrantha* leaves *Simplicia*.**

| Parameters | *Mikania micrantha* Leaf Simplicia (%) |
|---|---|
| Water content | 9.31 |
| Total ash content | 15.47 |
| Acid Insoluble ash content | 3.97 |
| Water-soluble extract | 18.45 |
| Ethanol soluble extract | 21.87 |

**Table 4. Physiochemical analysis of MMLE.**

| Parameters | MMLE (%) |
|---|---|
| Water content | 17.21 |
| Total ash content | 22.55 |
| Acid Insoluble ash content | 8.09 |

**Table 5. Phytochemical screening of *Mikania micrantha* leaves.**

| Phytochemical constituent | *Mikania micrantha* leaf | |
|---|---|---|
| | Simplicia | Extract |
| Alkaloids | + | + |
| Flavonoids | + | + |
| Tannins | + | + |
| Saponins | + | + |
| Glycosides | + | + |
| Terpenoids/Steroids | + | + |

+ Present.

### 3.2. Physical Examination of Nanogels Containing MMLE

The formulation shows a clear nanogel with good homogeneity, transparency, and dark green color. The pH of the nanogel was 6.1 ± 0.1. The particle size of the nanogel was in the range of 225-456 nm. The average particle sizes of MMLE nanogels are shown in Fig. (**1**).

### 3.3. Antibacterial Activity

Evaluation of the antibacterial activity was determined initially by the disc diffusion method against different bacteria. These bacterial strains are Gram-positive and Gram-negative species frequently encountered in infectious diseases [23]. The diameter inhibition zone is shown in Table **6**. The zone of inhibition of nanogel was higher than gel in *Staphylococcus aureus* and *Staphylococcus epidermis*. Statistically, there were significant differences between groups ($p$<0.05). However, the zone of inhibition of gel was higher than nanogel in *Escherichia coli*, but statically, there were no significant differences ($P$>0.05).

### 3.4. *In Vivo* Diabetic Wound Healing Study

The result of *In vivo* wound healing studies on the left and right backsides are represented in Tables **7** and **9**. From the result, it could be noticed that all treatment groups showed wound closure, as shown in Fig. (**2**). The percentage of wound closure of P2 (left side) and K2 (right side) are higher than other groups. The wound-healing effects in the

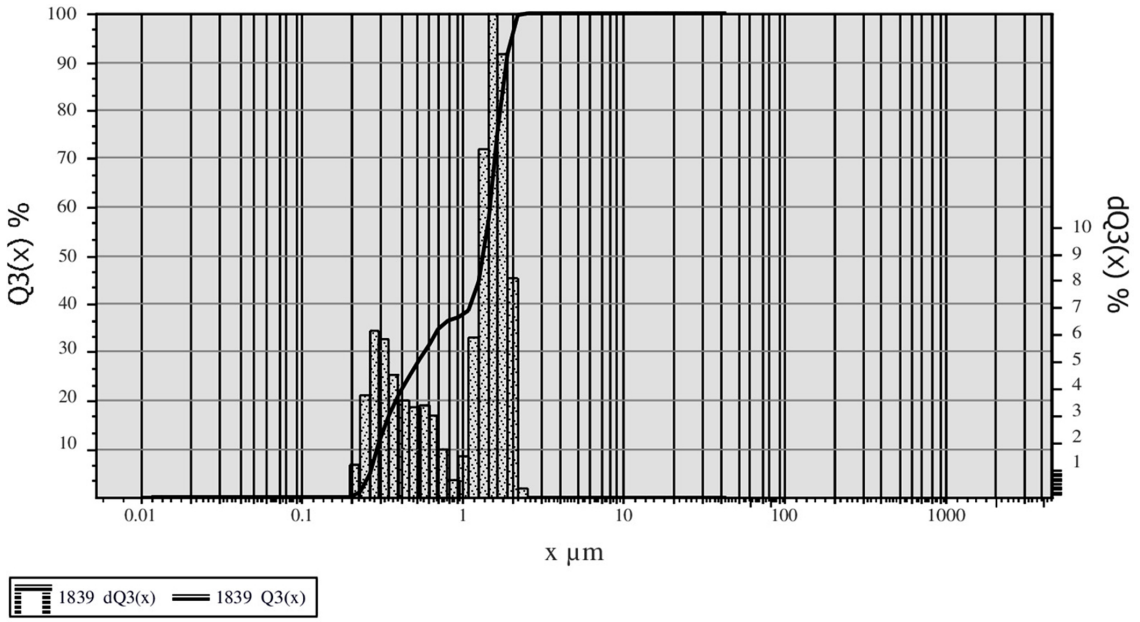


**Fig. (1).** The particle size average of nanogel containing MMLE.

**Table 6. Antibacterial activity (inhibition zones, mm).**

| Treatment Group | Zone of Inhibition (mm) | | |
|---|---|---|---|
| | ***Staphylococcus aureus*** | ***Staphylococcus epidermis*** | ***Escherichia coli*** |
| P1 | 9.2 ± 0.22 | 8.6 ± 0.59 | 8.7 ± 0.21 |
| P2 | 10.57 ± 0.26 | 9.73 ± 0.21 | 8.4 ± 0.1 |
| $P^{a,b}$ | 0.05 | 0.05 | 0.072 |

a. Kruskal Wallis.
b. Mann-Whitney.

**Table 7. Effect of treatment group on wound healing in the left backside.**

| Treatment Group | Rate of Wound Healing (day) Mean ± SD | | | | |
|---|---|---|---|---|---|
| | **1** | **3** | **5** | **7** | **14** |
| P1 | 0 | 38.21 ± 6.72 | 71.08 ± 7.08 | 72.92 ± 5.57 | 84.37 ± 6.54 |
| P2 | 0 | 52.58 ± 9.80 | 77.29 ± 7.26 | 85.83 ± 4.72 | 94.08 ± 2.33 |
| K1 | 0 | 12.92 ± 4.58 | 74.5 ± 7.17 | 82.71 ± 4.28 | 90 ± 1.58 |
| K2 | 0 | 3.33 ± 4.08 | 42.71 ± 9.30 | 61.04 ± 15.44 | 67.08 ± 5.34 |

**Table 8. Statistical analysis.**

| Between | | *pb (*day) | | | | |
|---|---|---|---|---|---|---|
| | | **1** | **3** | **5** | **7** | **14** |
| P2 | P1 | 1.000 | 0.020 | 0.126 | 0.005 | 0.008 |
| | K1 | 1.000 | 0.054 | 0.467 | 0.284 | 0.012 |
| | K2 | 1.000 | 0.004 | 0.004 | 0.004 | 0.004 |
| $p^a$ | | 1.000 | 0.001 | 0.002 | 0.001 | 0.000 |

$p^a$ = Kruskal Wallis.
$p^b$ = Mann-Whitney.

**Table 9. *In vivo* wound healing in the right backside.**

| Treatment Group | Rate of Wound Healing (day) Mean ± SD | | | | |
|---|---|---|---|---|---|
| | **1** | **3** | **5** | **7** | **14** |
| P1 | 0 | 34.58 ± 7.13 | 73.33 ± 4.08 | 81.04 ± 4.63 | 84.37 ± 4.86 |
| P2 | 0 | 50.5 ± 7.58 | 78.54 ± 3.10 | 85.83 ± 3.41 | 92.79 ± 3.81 |
| K1 | 0 | 13.33 ± 8.16 | 80.00 ± 3.16 | 84.5 ± 3.00 | 94.12 ± 1.61 |
| K2 | 0 | 2.50 ± 2.74 | 54.33 ± 13.93 | 63.67 ± 4.88 | 64.37 ± 8.51 |

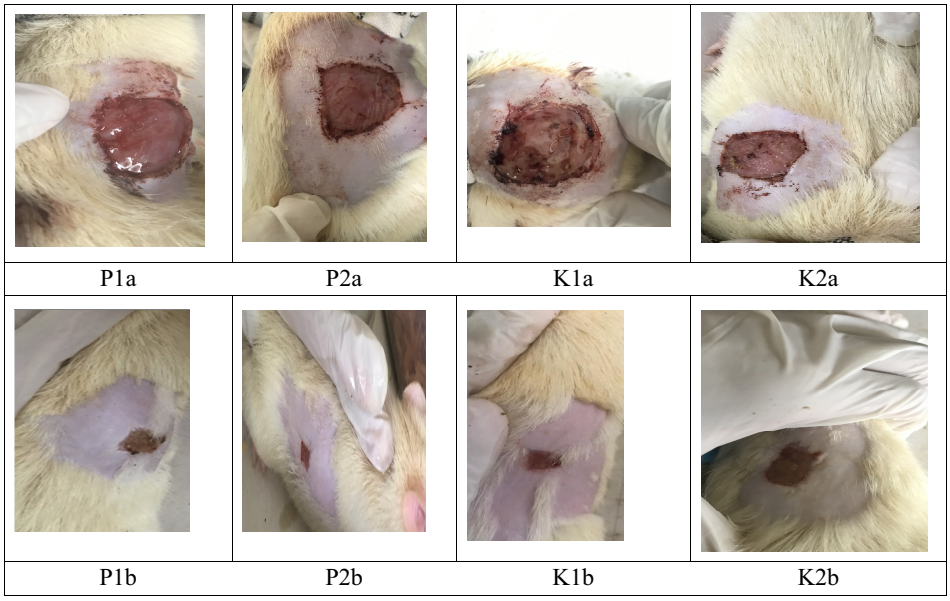


**Fig. (2).** The representative images of the wounds before (**a**) and after (**b**) treatment in hyperglycemic rats. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

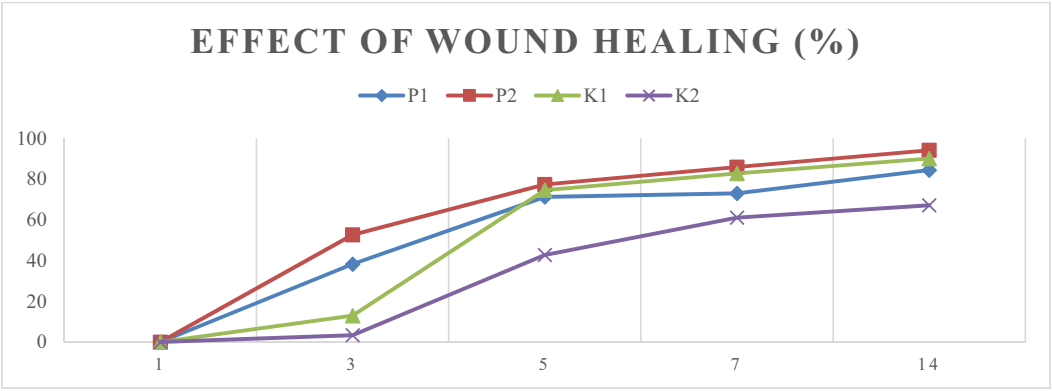


**Fig. (3).** Wound healing effect in the left backside. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

left and right backsides are shown in Figs. (**3** and **4**). Statically, there were significant differences between P2 with K2 and P1 ($P$<0.05), except in day 0 and day 3 observation ($P$>0.05), but there were no significant differences between P2 with K1 ($P$>0.05), except on day 14 observation ($P$<0.05) (Table **8**) in the left backside. In contrast, there were significant differences between P2 with P1, K2 ($P$<0.05). However, there were no significant differences between P2 with K1 ($P$>0.05), except on day 0 and day 3 ($P$<0.05) (Table **10**). From this result, it could be seen that MMLE nanogels (P2) have the same effect as cutimed® gel (K1), and it was better than MMLE gels (P1) and base gels (K2). It also showed that P2 has time action of effect better than others.

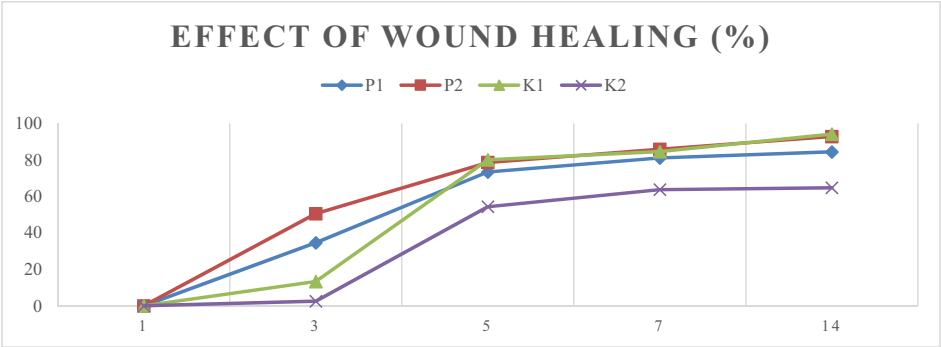


**Fig. (4).** Wound healing effect in the right backside. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

**Table 10. Statistical analysis.**

| Between | | *pb* (day) | | | | |
|---|---|---|---|---|---|---|
| | | **1** | **3** | **5** | **7** | **14** |
| P2 | P1 | 1.000 | 0.010 | 0.051 | 0.088 | 0.012 |
| | K1 | 1.000 | 0.004 | 0.393 | 0.454 | 0.868 |
| | K2 | 1.000 | 0.003 | 0.004 | 0.004 | 0.004 |
| *p*[a] | | 1.000 | 0.000 | 0.001 | 0.002 | 0.000 |

pa = Kruskal Wallis.
pb = Mann-Whitney.

## 4. DISCUSSION

*Mikania micrantha* is a medicinal plant that is used as a herbal medicine. This is due to the content of biological and pharmacological compounds. MMLE is used traditionally for dressing and healing and for sores by our ancestors by squeezing and affixing it to the area [24]. Standardization of extracts is important to ensure the quality of extract as raw material based on physicochemical and phytochemical screening that are responsible for the therapeutic activities of the plants (Tables **3**-**5**) [25, 26].

Nanogel is a hydrogel dosage formed with nanotechnology that has been proven to be used to develop and improve its application in herbal preparations. Nanogels possess the characteristics of both hydrogels and nanomaterials with a diameter ranging from 1 nm to 1000 nm [14]. The formulation of nanogels qualifies the range of particle size. The pH of nanogels was in the normal pH range of the skin and would not produce any skin irritation. The physiological pH of the skin in the range is 4.5-6.5 [27].

Most infected wounds are caused by polymicrobial and are generally contaminated by pathogens found in the immediate environment, such as the endogenous microbes that live in mucous membranes and microflora on adjacent skin. Compared to other microorganisms, bacteria are the main cause of wound infection in the skin, although other microorganisms such as fungi have been involved in certainly mixed infections. In the initial stages of chronic wound formation, *Staphylococcus aureus* and *E. coli* are predominant [28]. Hyperglycemia has been a strategic medium for bacterial growth. The bacteria found most in diabetic ulcer patients are *Staphylococcus* sp. (92.9%), *E. coli* (42.1%) [29]. Table **4** showed P1 and P2 have antibacterial activity for *Staphylococcus aureus*, *Staphylococcus epidermis*, *and E. coli.* A zone of inhibition measuring more than 8 mm signifies that bacteria are susceptible to sample [30]. MMLE contains tannins, flavonoids, and polyphenols, exhibiting potential antibacterial activities [26, 31, 32]. Polyphenols have toxicity towards microbial enzymes, while structural features of flavonoids may help gain entry into the bacterial cell, which eventually leads to multiple component inactivation [11].

Nanogels are very effective in increasing the drug payload in the target site and for controlling the leaking tendency of other nanocarriers [14]. MMLE has a significant acceleration in wound healing on fibroblast cells even in a lower dose [24]. Histological studies suggest that MMLE improves the healing process on diabetic wounds in rats by increasing granulation tissue and collagen deposition [33]. For wound healing, collagen protein acts as a scaffold in connective tissue, and deposition of collagen results in increased tensile strength of the wound site [34]. MMLE contains alkaloids, terpenoids, and steroids. Alkaloids can accelerate the initial phase by stimulating the formation of the fibroblast phase. Steroids can help regeneration of new skin cells in the open wound. Terpenoids can help the wound healing process [10]. In a wound healing study in male Wistar rats, an ointment from *M. micrantha* showed a moderate rate of wound healing, probably by enhancing collagen [34].

## CONCLUSION

Nanogel containing MMLE has potential as a treatment for diabetic wound healing and a better time of action. It has

a percentage of wound healing in the range of 92.79 ± 3.81 to 94.08 ± 2.33 among 14 days observed. It also has antibacterial activity, that is, against *Staphylococcus aureus*, *Staphylococcus epidermis*, and *E. coli.*

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was conducted with permission from the Animal Research Ethics Committee, University of Sumatera Utara, Medan, Indonesia. (No. 0226/KEPH-FMIPA/2019).

## HUMAN AND ANIMAL RIGHTS

No humans were used in the study. All the animal experiments were performed in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animals.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.

## FUNDING

This research was funded by the Ministry of Research and Technology and The Higher Education Republic of Indonesia, Research and Community Service, University of Sumatera Utara, grant number: TALENTA 2019 No.386/ UN5.2.3.1/PPM/KP-TALENTA/2019).

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

This research was supported by the Ministry of Research and Technology and The Higher Education Republic of Indonesia, Research and Community Service, University of Sumatera Utara.

## REFERENCES

[1] International Diabetes Federation. Diabetes facts & figures. https://diabetesatlasorg/ 2019. Available from: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html (accessed May 26, 2020).

[2] Fransisca K. Awas Pankreas Rusak Penyebab Diabetes. Jakarta: Cerdas Sehat 2013; pp. 5-7.

[3] American Diabetes Association. Diagnosis and Management of Diabetic Foot Complications. Arlington: Healogics Inc and Oraganogenesis Inc 2018; p. 5.

[4] Aly UF. Preparation and evaluation of novel topical gel preparations for wound healing in diabetics. Int J Pharm Pharm Sci 2012; 4(4): 76-7.

[5] Singh AV, Aditi AS, Gade WN, Cats T, Lenardi C, Milani P. Nanomaterials: new generation therapeutics in wound healing and tissue repair. Curr Nanosci 2010; 6(6): 577-86. http://dx.doi.org/10.2174/157341310793348632

[6] Chadwick P, Edmonds M, McCardle J, Armstrong D. Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers. London: Wound International 2013; pp. 1-20. Available from: www.woundsinternational.com

[7] Bahramsoltani R, Farzaei MH, Rahimi R. Medicinal plants and their natural components as future drugs for the treatment of burn wounds: an integrative review. Arch Dermatol Res 2014; 306(7): 601-17. http://dx.doi.org/10.1007/s00403-014-1474-6 PMID: 24895176

[8] Devi K, Santhi M, Umadevi U. Phytochemical analysis of selected wound healing medicinal plants. Int J Pharm Sci Res 2017; 8(2): 852. http://dx.doi.org/10.13040/IJPSR.0975-8232.8(2).852-55

[9] Bahmani M, Asadi-Samani MA. Review of the most important medicinal plants effective on wound healing on ethnobotany evidence of Iran. J Inj Inflamm 2016; 1(1): E07.

[10] Fernandes A, Rizki M, Sigit S. Rayan. karakterisasi kimia dan potensi daun tanaman akar bulon (*Micania micrantha* kunth) sebagai obat luka tradisional. Jurnal Penelitian Ekosistem Dipterokarpa 2018; 4(2): 109-16. http://dx.doi.org/10.20886/jped.2018.4.2.109-116

[11] Sheam MM, Haque Z, Nain Z. Towards The Antimicrobial, Therapeutic and Invasive Properties of *Mikania micrantha* Kunth: A Brief Overview. J Adv Biotechnol Exper Therapeut 2020; 3(2): 92-101. http://dx.doi.org/10.5455/jabet.2020.d112

[12] Bonifácio BV, Silva PB, Ramos MAS, Negri KMS, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. Int J Nanomedicine 2014; 9: 1-15. http://dx.doi.org/10.2147/IJN.S52634 PMID: 24363556

[13] Ghosh V, Saranya S, Mukherjee A, Chandrasekaran N. Cinnamon oil nanoemulsion formulation by ultrasonic emulsification: investigation of its bactericidal activity. J Nanosci Nanotechnol 2013; 13(1): 114-22. http://dx.doi.org/10.1166/jnn.2013.6701 PMID: 23646705

[14] Molina M, Asadian-Birjand M, Balach J, Bergueiro J, Miceli E, Calderón M. Stimuli-responsive nanogel composites and their application in nanomedicine. Chem Soc Rev 2015; 44(17): 6161-86. http://dx.doi.org/10.1039/C5CS00199D PMID: 26505057

[15] Chopade SS. Design and *in-vitro* evaluation of tenoxicam nanogel containing noveon polymer. IJPSR 2019; 10(12): 5430-4. http://dx.doi.org/10.13040/IJPSR.0975-8232.10(12).5430-34

[16] Sumalatha K, Rao AS, Latha P. 2014 design and *in vitro* evaluation of nanogel containing mentha piperita. Am J Biol Pharmaceuti Res 2014; 1(3): 136-9. Available from: https://www.researchgate.net/publication/284173316

[17] Collins CH, Lynes PM, Grange JM. Microbiological Methods, 7th Edn. Britain: Butterwort-Heinemann Ltd 1995; pp. 175-90.

[18] Govindasamy C, Srinivasan R. *In vitro* antibacterial activity and phytochemical analysis of *Catharanthus roseus* (Linn.) G. Don. Asian Pac J Trop Biomed 2012; 2(1): 155-8. http://dx.doi.org/10.1016/S2221-1691(12)60148-8

[19] Romero-Cerecero O, Zamilpa A, Díaz-García ER, Tortoriello J. Pharmacological effect of *Ageratina pichinchensis* on wound healing in diabetic rats and genotoxicity evaluation. J Ethnopharmacol 2014; 156: 222-7. http://dx.doi.org/10.1016/j.jep.2014.09.002 PMID: 25218321

[20] Habibi G, Fereydounil T, Amini M, *et al.* Evaluation of the wound healing potency of myr myrtus communis aqueous extract on diabetic rat. J Res Med Dent Sci 2018; 6(6): 70-4.

[21] Sandeep B, Vijaykumar R, Kiran SR. Evaluation of wound healing activity of *Cyperus rotundus* essential oil. Int J Pharm Pharm Sci 2012; 4(1): 224-6.

[22] Bambal VC, Wyawahare NS, Turaskar AO, Deshmukh TA. Evaluation of wound healing activity of herbal gel containing the fruit extract of *Coccinia indica* wight and Arn. (Cucurbitaceae). Int J Pharm Pharm Sci 2011; 3(4): 319-22.

[23] Bereksi MS, Hassaine H, Bekhechi C, Abdelouahid DE. Evaluation of antibacterial activity of some medicinal plants extracts commonly used in algerian traditional medicine against some pathogenic bacteria. Pharmacogn J 2018; 10(3): 507-12. http://dx.doi.org/10.5530/pj.2018.3.83

[24] Sarimah MN, Mizaton HH. The wound healing activity of mikania micrantha ethanolic leaf extract. J Fundam Appl Sci 2018; 10(6): 425-37.

http://dx.doi.org/10.4314/jfas.v10i6s.7

[25] Departemen Kesehatan Republik Indonesia. Farmakope Herbal Indonesia. (1st ed.). Jakarta: Badan Pengawasan Obat dan Makanan 2008; pp. 169-71.

[26] Matawali A, Ping L, Siew H, Gansau J. Antibacterial and phytochemical investigations of mikania micrantha H.B.K. (Asteraceae) from sabah, Malaysia. Trans Sci Technol 2016; 3(2): 244-50. Available from: https://www.researchgate.net/publication/305858835

[27] Tranggono RI, Latifah F. Buku pegangan ilmu pengetahuan kosmetik. Jakarta: PT Gramedia Pustaka Utama 2007; pp. 29-31.

[28] Sarheed O, Ahmed A, Shouqair D, Boateng J, Eds. Antimicrobial dressing for improving wound healing. In: Alexandrescu V, ed. Wound healing. London, UK: IntechOpen 2016. http://dx.doi.org/10.5772/63961

[29] Nur A, Marisa N. Gambaran Bakteri Ulkus Diabetikum di Rumah Sakit Zainal Abidin dan Meuraxa Tahun 2015. Buletin Penelitian KesehatanI 2016; 44(3): 187-96. http://dx.doi.org/10.22435/bpk.v44i3.5048.187-196

[30] Saquib SA, AlQahtani NA, Ahmad I, Kader MA, Al Shahrani SS, Asiri EA. Evaluation and comparison of antibacterial efficacy of herbal extracts in combination with antibiotics on periodontal pathobionts: an *in vitro* microbiological study. Antibiotics (Basel) 2019; 8(3): 1-12. http://dx.doi.org/10.3390/antibiotics8030089 PMID: 31266146

[31] Pérez-Amador MC, Ocotero VM, Balcazar RI, Jiménez FG. Phytochemical and pharmacological studies on *Mikania micrantha* H.B.K. (asteraceae). Phyton 2010; 79: 77-80. http://dx.doi.org/10.32604/phyton.2010.79.077

[32] Harahap NI, Nainggolan M, Harahap U. Formulation and evaluation of herbal antibacterial gel containing ethanolic extract of *Mikania micrantha* kunth leaves. Asian J Pharm Clin Res 2018; 11(3): 429-31. http://dx.doi.org/10.22159/ajpcr.2018.v11i3.22211

[33] Samsulrizal N, Suhaimi NA, Sopian NFA, Hatta SKM, Jamil NM. Hypoglycaemic, antioxidant and wound healing activities of mikania micrantha leaves extract in normal and alloxan-induced diabetic rats. Sci Lett 2013; 7(2): 6-10.

[34] Rangaraj A, Harding K, Leaper D. Role of collagen in wound management. Wounds UK 2011; 7(2): 54-63.