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Oral Ulcer Healing Activity of Lemon Pepper Ethanol Extract Gel in Streptozotocin-Induced Diabetic Wistar Rats

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Abstract

Diabetes mellitus (DM) is a metabolic condition where the body's ability to produce and utilize insulin is impaired; thus, wound healing process is slower than usual in patients with DM. Lemon pepper has both antioxidant and anti-inflammatory properties. This study aimed to investigate the effect of topical application of lemon pepper fruit ethanol extracts on the healing process of oral traumatic ulcers in diabetic rats. This study was performed at the Pharmacology Laboratory, Faculty of Medicine, Universitas Prima Indonesia from September 2021–October 2021. Thirty males diabetic Wistar rats were thermally injured on the lower labial mucosa and divided into five groups: control, standard, and lemon pepper gel 5%, 7.5%, and 10% groups. The ulcer size was measured after injury and on the 7th and 14th day. On the last day, all rats underwent both routine blood count and histology study for oral ulcer tissue. On the 14th day, all treatment groups showed some significant difference wound contraction, with the highest tendency of wound contraction seen in both lemon pepper gel 10% and standard groups (62.50%. p-value =0.001). The improvement of wound contraction was also supported by reduced white blood cell count (p-value<0.05) in routine blood count and regeneration of epidermis and dermis tissues in the histology study. Hence, it can be concluded that the lemon pepper extract gel in all concentrations has good physical stability and the lemon pepper gel with the highest concentration group presents the best ulcer healing activity compared to other concentrations and has similar ulcer healing activity as the standard group that receives Kenalog® in Orabase.

Keywords: Diabetes mellitus, lemon pepper, oral ulcer, ulcer healing

Introduction

An oral ulcer is a lesion characterized by discontinuity of the epithelial layer across the basement membrane and affects the lamina propria. Based on the causes, the types of oral ulcers are varied, including acute and chronic conditions, benign and malignant diseases, and localized and systemic manifestations. Pain while eating, swallowing, or speaking might disturb a patient's daily routines and quality of life.[1]

Traumatic ulcers are most commonly produced by thermal, mechanical, chemical, or electrical trauma to the oral mucosa and are most commonly encountered on non-keratinous surfaces such as the buccal/labial mucosa, tongue, lips, and hard or soft palate. These ulcers are characterized by a yellowish-white necrotic pseudomembrane with elevation and erythematous margins. It usually takes 7 to 14 days for traumatic ulcers in the mouth to heal.[2]

The objectives of ulcer therapy are to reduce the pain and promote healing, which can be achieved by eliminating the risk factor and applying topical ointments such as topical corticosteroids as the first line of ulcer therapy because they are inexpensive efficacious safe. Inflammatory response, cell proliferation, and production of the extracellular matrix components and the post-healing period, known as remodeling, are the three stages of cell and biochemical processes that are closely linked in

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wound repair.[3,4]

Remodeling is the third phase of healing, which starts two to three weeks after the initiation of the lesion and can extend a year or more, which aims to maximize tensile strength by reorganizing, degrading, and re-synthesizing the extracellular matrix. At this phase in the healing process, an attempt is made to restore normal tissue structure, and the granulation tissue is gradually remodeled, resulting in scar tissue that is less cellular and vascular and has a progressive rise in collagen fiber concentration.[5]

Diabetes mellitus (DM) is a metabolic disorder in which the human body fails to synthesize or utilize insulin, a hormone necessary to degrade sugar, starches, and other carbohydrates into energy. Protease imbalance, cytokines, and growth factors can all induce ulcers in people with diabetes mellitus (DM). With persistent hyperglycemia and oxidative stress, vascular diseases can lead to tissue hypoxia, resulting in decreased vascular endothelial growth factor (VEGF) levels and the accumulation of advanced glycosylation end products in the tissue. Angiogenesis is facilitated by the presence of VEGF. Reduced fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) flow in the fibroblast synthesis and collagen synthesis process promotes cell death and enhanced collagenase activity, and as a result, wound healing takes longer [6].

Lemon pepper, also known as andaliman or *Zanthoxylum acanthopodium* DC., is an indigenous plant in the North Sumatera area that has long been utilized in Bataknese community. In some previous studies, lemon pepper is an antioxidant, antibacterial against infections, anti-inflammatory, and anti-acne agent. Lemon pepper's antioxidant effects are related to the presence of the flavonoid component[7]. Alkaloids, flavonoids, glicoside, saponins, tanins, triterpene/steroids, and glicoside anthraquinone are some of the bioactive chemicals found in lemon pepper fruit extracts [8]. Due to these phytochemicals, some previous study showed that the lemon pepper extract has antidiabetic activity by oral administration which moreover may also prevent the microvascular complication against the liver and kidney.[9–11] On the other hand, other study by Purnama et al also reported that the lemon pepper essential oil has a wound healing activity against the burn wound in non-diabetic rats[12]. However, none of these previous studies that were investigated the wound healing activity against the oral ulcer in diabetic condition. Hence this study was aimed to examine the effect of topical application of lemon pepper fruit extracts to the healing process of oral traumatic ulcers in diabetic rats.

Methods

This study was an experimental study with a post-only group control design. This study was performed at Pharmacology Laboratory, Faculty of Medicine, Universitas Prima from September 2021–October 2021. All procedures have been approved by Health Research Ethics Committee Universitas Prima Indonesia with letter no. 005/KEPK/UNPRI/VII/2021.

Some lemon peppers were obtained from a traditional Market in Medan. The lemon peppers were macerated with 70% ethanol solvent for seven days before being subsequently filtered and evaporated by a vacuum rotary evaporator at 40°C to obtain concentrated lemon peppers extract.[11]

Phytochemical screening investigated the presence of some phytochemicals like alkaloid, saponin, flavonoid, tannin, steroid, and terpenoid. Meanwhile, the total polyphenol compound content only determined the total phenol, flavonoid, and tannin content. Phytochemical screening and total polyphenols compound contents were performed based on the procedure described by Salim et al.[13]

Lemon pepper gel was made by suspending lemon pepper ethanol extract into the gel base. The gel base was made by mixing two different colloid systems, viz. SCMC (sodium CMC) and carbomer Gel. SCMC was made by dissolving 3 grams Na-CMC into 50 mL distilled water. Meanwhile, Carbomer gel was made by dissolving a gram of carbomer powder into 50 ml distilled water. Propyl and Methyl Parabens acted as the preservative. Thus, Propyl paraben, methyl paraben, and lemon pepper extract were suspended into Propylene glycol as the dispersing medium. Finally, this mixture, SCMC, and carbomer were stirred until homogenous to form a gel.[14,15]

Characteristics of all lemon pepper gels were evaluated to look for physical stability by Freeze-Thaw methods. Each cycle consisted of the freezing and thaw phase. The freezing phase was performed by serving all gels at 4°C for 24 hours. Meanwhile, the thaw phase followed the freezing phase for the next 24 hours at 40°C. This study was used freeze-thaw methods for six cycles. Furthermore, all lemon pepper gels were evaluated for the organoleptic, homogeneity, pH, and spreading ability with or without a load in

each cycle.[16]

This study was used 30 male Wistar rats that have been adapted for seven days. All rats received standard rat pellets amount of 10% from rat's body weight and drank water freely at room temperature. All Wistar rats were injected intraperitoneally with a single dose of 50 mg/kgBW streptozotocin (Cat No. A10868-500; Sciencewerke). After three days, all rats measured the blood glucose level, and all rats with blood glucose levels higher than 200 mg/ dL were included as the animal trial to randomized into five different groups. Furthermore, all rats were injured the lower lips mucose by applying Ball Burnisher Tip (thermal injury) under the anesthesia condition. The anesthesia was performed by intraperitoneal injection of 0.1 mL/10 gBW of rodent anesthesia (ketamine in sterile normal saline).

Thirty male Wistar rats suffering from DM with induced ulcers on the lower labial mucosa were grouped into five groups, consisting of six rats per group. These groups were control, standard, lemon pepper gel 5%, 7.5%, and 10% that were received gel base, kenalog® in orabase (0.1% triamcinolone acetonide), lemon pepper gel 5%, 7.5%, and 10% once a day for 14 days, respectively.

These gels were applied directly into the oral ulcer in all rats according to their groups of treatment which were has been described. Kenalog ® in Orabase was used as standard drug because it contains triamcinolone acetonide, corticosteroid, that was first line of the first line of ulcer therapy.[3]

Gel base in control group was made by combining 2 different gel phase that were SCMC (sodium CMC) gel and carbomer gel. SCMC gel was made by dissolving 3 grams of Na-CMC into 50 mL of distilled water and Carbomer Gel was made by dissolving 1 gram of Carbomer 940 into 50 mL of distilled water. Meanwhile, Propylene glycol acts as a dispersing medium for the lemon pepper extract, propyl and methyl paraben. Then the two phase of gel (SCMC gel and carbomer gel) were stirred until homogeneous. Finally, the propyl glycol which has been mixed with the extract, methyl paraben, and propyl paraben is stirred together. Moreover, the lemon pepper gel 5%, 7.5%, and 10% were made by mixing 2.5 grams, 3.75 grams, and 5 grams lemon pepper ethanol extract into 50 grams gel base, respectively.[2]

The observations of ulcer size were performed immediately after the injury, 7th, and 14th days after the ulcer creation. The ulcer size was measured by vernier caliper in milimeter. These ulcer size data were used to determine the wound contraction. The wound contraction was obtained by divided difference between initial wound size with specific measurement day wound size into initial wound size and multiple with 100% to express the wound contraction in percent (%).

Other than the ulcer size, this study also looks for routine blood count and ulcer tissue histology study on the 14th day. These procedures used whole blood and ulcer tissue obtained from the sacrificed rats. All rats were sacrificed on 14th day by chloroform inhalation in a closed chamber. After that, the anesthetized rat was fixed into paraffin blocked to excise all ulcer tissues and withdraw blood from intracardiac puncture into the rats' thorax by 5 mL syringe. All excised tissues were sustained into 10% buffer formalin solution until all tissues were processed into hematoxylin and eosin staining, and the obtained blood was filled into a red-colored blood tube. The histology study was based on the histology study procedure in the Histology Laboratory of Universitas Prima Indonesia. Meanwhile, the routine blood count was performed in the regional health laboratory (*Laboratorium Kesehatan Daerah*), Medan, North Sumatera.

In the beginning, descriptive statistics analyzed all data. After that, all data were also undergone normality analysis. If data distribution was normal, all data were analyzed by one-way ANOVA followed by Post Hoc Test Tukey HSD and expressed as mean±SD; otherwise, if data distribution was not normal, all data were analyzed Kruskal-Wallis followed by Mann-Whitney and expressed as median (min-max). Moreover, this study used signification (p-value) lower than 0.05 that considered as statistically significant.

Results

This study used some lemon pepper fruits obtained from a traditional market in Medan, North Sumatera. These lemon pepper fruits were identified in Herbarium Medanense, a laboratory under Faculty of Mathematics and Science, Universitas Sumatera Utara. The result of identification showed that these lemon pepper fruits had a scientific name as *Zanthoxylum acanthopodium*. After that, these lemon pepper fruits were extracted and the obtained extract was used for phytochemicals screening, and the

results as described in Table 1.

Based on Table 1, the lemon pepper ethanol extract consisted of some phytochemicals included alkaloids, flavonoid, tannin, and steroid/triterpenoid. Moreover, this study also determined the total content of phenol, flavonoid, and tannin. Total phenolic, tannin, and flavonoid contents were described in Table 2.

Based on Table 2, a lemon pepper ethanol extract has the highest content of tannin (37.73 TAE mg/ gram extract), followed by phenol (34.33 GAE mg/ gram extract), and the lowest one was flavonoid (5.52QE mg/ gram extract).

After that, the obtained lemon pepper ethanol extract was formulated into some concentrations of gels (10%, 7.5%, and 5%). These lemon pepper gels had been evaluated for physical stability and characteristics (organoleptic, general appearance, pH, and spreading ability with or without load). Moreover, these characteristics were measured at six different times (cycles) to look for physical stability over time. In the beginning, lemon pepper gel underwent organoleptic evaluation. Based on the organoleptic evaluation, it can be seen that all concentration lemon pepper gels were stabile over six different times. All lemon pepper gels were a semi-solid form with a characteristic odor and dark brown color. These forms, odor, and color were stabile over six different times.

Moreover, this study also evaluated the general appearance of all lemon pepper gels, and the general appearance of all lemon pepper gels was homogenous. All lemon pepper gels were also stabile at six different times. All lemon pepper gels had a homogenous appearance over the six different times.

Another characteristic evaluated in this study was pH as the chemical properties of the gel. The pH of all lemon pepper gels ranged from 6.0–6.2, and this pH was stable for six different times. The lowest pH was found in 5% lemon pepper gel (6.0), followed by 7.5% lemon pepper gel (6.1), and the highest one was 10% lemon pepper gel (6.2).

Other than the pH, this study also evaluated the spreading ability of gel with or without load. The spreading ability of all lemon pepper gels ranged from 3.3–3.5. The widest spreading ability was found in the 5% lemon pepper gel (3.5), followed by 7.5% lemon pepper gel (3.2), and the narrowest was shown by 10% lemon pepper gel (3.3). This spreading ability value from all gels was constant for six different times. Finally, the spreading ability was modified by adding a load of 100 grams into this test, and the spreading ability became wider than without load. These spreading abilities with a load of 100 grams ranged from 5.1–5.8 cm. The widest spreading ability with load was found in 5% lemon pepper gel (5.8), followed by 10% lemon pepper gel (5.5), and the narrowest one was found in 7.5% lemon pepper gel that was 5.1.

After evaluating the characteristic of all lemon pepper gels, these gels were used to investigate their ulcer healing activity. Evaluating wound healing activity from lemon pepper gel used wound size and wound contraction as the parameter. A comparison of wound size in all groups was described in Table 3.

Table 1 Phytochemical Screening

Phytochemical	Reagents	Results
Alkaloids	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponins	Aquadest + Alcohol 96%	-
Flavonoid	FeCl3 5%	+
	$Mg_{(s)} + HCl_{(p)}$	-
	NaOH 10%	-
	$H_2SO_{4\ (p)}$	-
Tannin	$FeCl_3$ 1%	+
Steroids and terpenoids	Salkowsky	-
	Liberman Bouchard	+

Table 2 Total Phenolic, Flavonoid, and Tannic Acid

Phytochemicals	Phytochemical Content
Phenol (GAE mg/gram extract)	34.33 ± 0.0
Tannins (TAE mg/gram extract)	37.73 ± 0.29
Flavonoids (QE mg/gram extract)	5.52 ± 0.0

GAE: gallic acid equivalent; TAE: tannic acid equivalent; QE: quercetin equivalent

Based on Table 3, there is a significant reduction of wound size among all treatment groups in first and second week, and it can be seen from the P-Value < 0.05 (P-Value = 0.001) in first and second week. In the first weeks, both gel lemon pepper at 7.5% (1.50 [1.20-2.00]) and 10% (1.50 [1.20-1.90]) showed a similar wound size reduction as good as the standard group (1.50 [1.20-2.10]). However, the lowest gel concentration that was Lemon Pepper Gel 5% (2.30 [2.30-2.50]) did not significantly reduce, like the standard group (1.50 [1.20-2.10]). The lowest gel concentration (2.30 [2.30–2.50]) showed a similar wound size reduction to the control group (2.50 [2.30–2.50]) that only received a gel base. After two weeks of intervention, the lowest gel concentration (2.10 [2.10–2.20]) showed no significant wound size reductions as good as the control group (2.20 [2.10–2.40]). The highest gel concentration that was lemon pepper gel 10% (0.80 [0.50–1.30]) constantly reduced wound size like the standard group (0.80 [0.40–1.80]).

Meanwhile, the moderate gel concentration still reduced the wound size better than the control group, but it was not as good as the standard or highest gel concentration group. This study also investigated the wound contraction shown as a percentage other than the wound size. A comparison of wound contraction was described in Table 4.

Based on Table 4, it can be seen that the wound contraction also showed a similar result to the wound size. The wound contraction at the first and second week significantly decreased in all groups, and it can be seen from the p-value <0.05 (p-value=0.001). In the first week, the last two

Table 3 Comparison of Wound Size in All Groups

Group	Wound Size (mm)		
	0 week	1st Week	2nd Week
Control	4.00 (4.00–4.00)	2.50 (2.30–2.50)[a]	2.20 (2.10–2.40)a
Standard	4.00 (4.00–4.00)	1.50 (1.20–2.10)b	0.80 (0.40–1.80)[b]
Lemon pepper gel 5%	4.00 (4.00–4.00)	2.30 (2.30–2.50)[a]	2.10 (2.10–2.20)[c]
Lemon pepper gel 7.5%	4.00 (4.00–4.00)	1.50 (1.20–2.00)[b]	1.40 (1.10–1.80)[b]
Lemon pepper gel 10%	4.00 (4.00–4.00)	1.50 (1.20–1.90)[b]	0.80 (0.50–1.30)b
P-value	1.000	0.001	0.001

Data were expressed as Median (Min-Max); p-value was obtained from Kruskal-Wallis test; the different superscript in the same column are significantly difference at p-value <0.05 based on Mann-Whitney test

Table 4 Comparison of Wound Contraction in All Groups

Group	Wound Contraction (%)	
	1st week	2nd Week
Control	37.50 (37.50–42.50)[a]	45.00 (40.00–47.50)[a]
Standard	62.50 (47.50–70.00)[b]	80.00 (55.00–90.00)[b]
Lemon pepper gel 5%	42.50 (37.50–42.50)[a]	47.50 (45.00–47.50)[a]
Lemon pepper gel 7.5%	62.50 (50.00–70.00)[b]	65.00 (55.00–72.50)[c]
Lemon pepper gel 10%	62.50 (52.50–70.00)[b]	80.00 (67.50–87.50)[b]
P-value	0.001	0.001

Data were expressed as Median (Min-Max); p-value was obtained from Kruskal-Wallis test; the different superscript in the same column are significantly difference at p-value <0.05 based on Mann-Whitney test

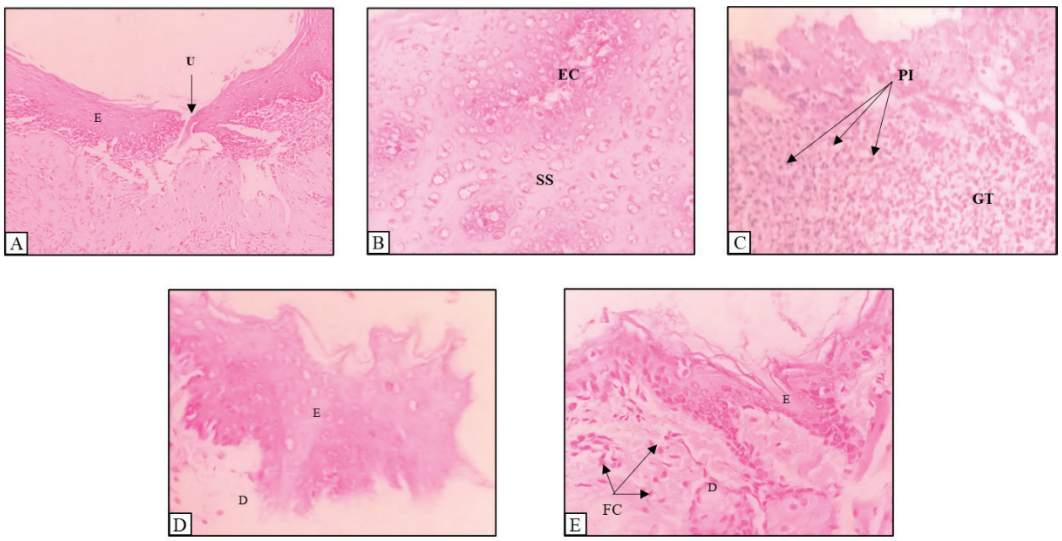

Figure Histology of Skin Tissue in All Groups. Stain: H&E. Magnification: 40x

(A) Standard Group; (B) Control Group; (C) Lemon Pepper Gel 5%; (D) Lemon Pepper Gel 7.5%; (E) Lemon Pepper Gel 10%. Ulcer Tissue (U); Epidermis (E); Dermis (D); Stratum Spinosum in Epidermis (SS); Granulation Tissue (GT); Inflammation Cells Infiltration (PI); Epidermal Cleft (EC); Fibroblast Cells (FC)

highest concentration gels wound contraction which were lemon pepper gel 7.5% and 10%, and standard groups were 62.50%, followed by the lemon pepper gel 5% that was 42.50%, and the lowest wound contraction was shown by the control group that was 37.50%. Next week, the distribution of this wound contraction was similar to the first week. The highest wound contraction was shown by the standard and lemon pepper gel 10% that was 80%, followed by the lemon pepper gel 7.5% (65%), lemon pepper gel 5% (47.50%), and the lowest one shown by the control group which was 45%.

This study evaluated not only the wound size but also the blood for the routine blood test. The routine blood count in all rats were described in Table 5.

Based on Table 5, hemoglobin and the number of red blood cells did not show any significant differences in all groups, and it was shown by the p-value>0.05. However, the white blood cells, leucocytes, showed some significant differences among each group. The control group and lemon pepper gel 5% groups did not show any significant differences in the average WBC number, but the WBC number from these groups was significantly higher than other groups. It can be seen from the superscript in the WBC column, which comes from Post Hoc Test Tukey HSD. Moreover, it can be seen that the highest WBC number was found in the control group, which was 10.30 x 10^3/mm^3, followed by lemon pepper gel 5%, 10%, and 7.5%, and the lowest WBC number was found in the standard group which

Table 5 Comparison of Routine Blood Test Result in All Groups

Group	HB (mg/dl)	RBC (x 10^6/ mm^3)	WBC (x 10^3/ mm^3)
Control	6.83 ± 0.75	11.58 ± 2.46	10.30 ± 2.40a
Standard	6.71 ± 0.84	11.00 ± 2.50	3.30 ± 0.72b
Lemon pepper gel 5%	6.91 ± 0.80	11.48 ± 2.42	8.35 ± 0.23a
Lemon pepper gel 7.5%	6.89 ± 0.83	10.56 ± 2.06	3.52 ± 0.46b
Lemon pepper gel 10%	6.99 ± 0.86	11.62 ± 2.44	4.54 ± 0.11b
P-Value	0.988	0.944	< 0.05

was 3.30 x 10^3/mm^3. Finally, this study also evaluated the histology of ulcer tissues, and the histology view from these tissues was described in Figure 1.

Based on Figure 1, it can be seen that the standard groups showed the best wound healing activity that was shown by the regenerated epidermis and dermis tissue. The regenerated epidermis can be seen from the full layer of the epidermis, and the regenerated dermis can be seen from intact loose connective tissue consisting of fibroblast and extracellular matrix. Meanwhile, the control group showed the worst wound healing activity than other groups shown by the epidermal cleft and thickening stratum spinous; these pathology changes indicated an uncomplete epidermis regeneration. Moreover, the groups that received the lowest concentration gel showed inflammation cells infiltration (showed as a cell with DNA condenses in nucleus and shrunken into basophilic mass) in the granulation tissue that replaced the damaged epidermis and dermis tissue. It indicated an incomplete wound healing process. At the higher concentration gel, the epidermis and dermis tissue has been regenerated, but the density of extracellular matrix and fibroblast cells was not as good as the standard groups. On the other hand, the highest concentration gel showed a better epidermis and dermis regeneration than the last two concentrations. It can be seen from the complete epidermis and dermis tissue.

Discussion

This study answered the purpose of looking for the optimum gel preparation from lemon pepper fruit to treat the oral ulcer. In the beginning, this study evaluated the characteristics and stability of all lemon pepper gels, and this study showed that all gel preparation was optimum. Moreover, all lemon pepper gels were evaluated for the oral ulcer healing properties by in vivo study. This study also showed that all lemon pepper gels had wound healing activity against the oral ulcer in the Wistar rats. This wound healing activity was shown from the decrease of ulcer size and histology study. Interestingly, this study also showed good oral ulcer healing activity in diabetic rats induced by the 50 mg/kgBW of STZ.

This study was used the freeze-thaw method to evaluate the physical stability of the gel. This method freezes the gel at the 4°C that crystalizes both (oil and water), when the oil phase freezes ealier than the water phase. It will cause unstable gels to appear when all gels are thawed; this instability appearance may reveal oiling off, creaming, coalescence, partial coalescence, and thickening of gelatination. However, this study did not show any instability appearances in all lemon pepper gels that were constantly stable for six cycles of the freeze-thaw cycle [17].

The stability of all gels was evaluated from some parameters, viz. organoleptic profile, general appearance, pH, and spreading ability with or without load. The organoleptic and homogeneity of all lemon pepper gels had characteristic odors like a natural lemon pepper fruit, semi-solid form, dark-brown colored, and homogenous appearance that was stabile after six cycles of the freeze-thaw cycle. Moreover, another parameter also showed an optimum formulation. The pH was ranged from 6.0–6.2, which was normally ranged within 4.5–6.5. Meanwhile, the spreading ability with load for all gels ranged between 5.1–5.8, followed by the decrease of the gel concentration. A good gel preparation has a spreading ability between 5–7 cm, and all lemon pepper gels have a good spreading ability. The wider spreading ability indicates the good spread of the active compound in the skin's surface and increases the higher concentration of active compound to diffuse into the skin tissue.[18]

All lemon pepper gel showed an optimum gel preparation. Hence, all lemon pepper gels were easily applied to the ulcer. Moreover, these gels are also physically stable and prevent decreased efficacy over time. This gel contains HPMC 5% that acted as an emulsifier and suspending agent for the gel that did not have any pharmacology properties.

There are limited studies that look for lemon pepper extract's wound healing activity. However, an in vitro study performed by Yanti et al.[19] reported that the lemon pepper extract has a significant anti-inflammatory activity by inhibiting the expression of some inflammatory biomarkers in lipopolysaccharide-induced macrophages. On the other hand, Negi et al.[20] also reported a similar result; lemon pepper essential oil has antioxidant activity with IC_{50} Value 27.0±0.1 μg/mL and moderate antibacterial activity. Negi et al. also reported that this antioxidant activity was due to the presence of various phytochemicals like bornyl acetate, cymene, α-copaene, γ-terpinene, camphene, β-ocimene and linalool which were analyzed by GC-MS procedure. Furthermore, the latest study performed by Purnama et al. reported a similar result. Purnama et al.[12] reported that

the essential oil from the lemon pepper extract formulated as the ointment had a wound healing activity against the skin burn wound in non-diabetic rats.

It can be concluded that the lemon pepper extract gel at all concentrations had good physical stability. The highest concentration (10%) lemon pepper gel has the best ulcer healing activity in oral wounds, especially in the streptozotocin-induced diabetic rats' model, as good as the standard gel.

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