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Anti-inflammatory Gel for Diabetic Ulcers from Catappa Leaf Extract (*Terminalia catappa*)

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Abstract

Diabetes Mellitus (DM) is a metabolic disease characterized by elevated blood glucose levels (hyperglycemia) resulting from a disruption in the body's insulin system. This condition has an impact on patients, leading to the development of diabetic ulcers. Administration or application of medication to the wound can aid in the wound healing process. One natural substance that can be used is the leaves of the catappa tree (Terminalia catappa), which contain complex compounds such as flavonoids, tannins, saponins, steroids, and phenolic compounds. These compounds act as anti-inflammatory, antibacterial, antifungal, anticancer, antioxidant, antidepressant, antimicrobial, anticandidal, anti-helicobacter pylori, and antiulcer agen. This study focuses on the creation of an anti-inflammatory gel using an extract from catappa leaves (Terminalia catappa) for wound healing, particularly in diabetic patients, to enhance the bioavailability of active ingredients. This research is experimental research with laboratory testing, namely gel testing of catappa leaf extract through phytochemical tests, anti-inflammatory tests, antibacterial tests, and stability tests physical gel. Testing phytochemical test yielding positive results for the presence of flavonoids, saponins, phenols, and tannins. Anti-inflammatory test results showed best anti-inflammatory is T1 (with 25% extract) with the highest stability value of 99.7%. The results antibacterial testing, T3 (with 75% extract) is the best antibacterial with inhibition average 13.420 mm. Physical stability tests for the gel were conducted, including organoleptic assessment, spreadability, adhesion, homogeneity, and pH. The choice of gel formulation offers advantages due to its distribution ability, effective drug release on the skin, and good spreadability and adhesion.

Keywords: Catappa Leaf Extract, Anti-inflammatory Gel, Diabetic Ulcers

Full-length article *Corresponding author email: desakrara98@gmail.com*

1. Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by elevated blood glucose levels (hyperglycemia) due to impaired insulin function in the body [1]. In Indonesia, 25% of DM patients suffer from diabetic ulcers, and 85% of them require amputation. This occurs because 50% of DM patients experience neuropathy, resulting in the loss of sensitivity in certain areas, such as an inability to feel pain, cold, or heat [2]. In diabetic patients, the normal and complex wound healing process is disrupted in several stages, leading to chronic complications and even death [3]. The wound healing stages consist of interconnected phases: hemostasis, inflammation, proliferation, and remodeling [4].

People can live healthily with diabetes through control measures. One effort is preventing diabetic foot ulcers (Diabetic ulcers). In diabetic patients, there are often soft tissue and skin infections such as furuncles, abscesses, and gangrene. Gram-positive cocci aerobic germs generally cause acute skin infections such as cellulitis and abscesses. However, prolonged infection of the causative germs is usually polymicrobial in nature, consisting of gram-negative cocci, gram-positive bacilli, and anaerobic bacteria [5]. On wounds, Diabetes is commonly found bacteria Staphylococcus aureus causes infection. The onset of mutant Antibiotic-resistant S. aureus bacteria can be caused due to the use of the strain's inappropriate antibiotics, and improper doses, causing wounds to heal difficult. This thing makes people more interested in using herbal medicine, because the price is cheaper and easier to obtain [6]. When conducting early detection and treatment, adequate wounds can reduce the incidence of amputation. Care attitudes and behaviors Supported by knowledge of infection, it is expected to reduce the infection rate in wounds, so that the healing process in treatment can be optimal [7].

One natural ingredient useful in the pharmaceutical world is the catappa leaves (*Terminalia catappa*). This plant is abundant in Indonesia and often sheds its leaves. Several studies on catappa leaf extracts indicate that this natural substance can serve as an anti-inflammatory, antibacterial, antifungal, anticancer, antioxidant, antidepressant, antimicrobial, anticandidal, anti-helicobacter pylori, and antiulcer agent [8]. Catappa leaves contain alkaloids, steroids, triterpenoids, flavonoids, tannins, and saponins. Flavonoids,

tannins, and saponins have anti-inflammatory potential and accelerate wound healing [9].

The extract from catappa leaves is believed to assist in the healing process. The contained flavonoids can prevent inflammation and play a crucial role in maintaining capillary blood vessel permeability and resistance, often used in pathological situations where vessel wall permeability disruptions occur. Tannins enhance wound attraction during the healing process. Tannins have astringent effects that shrink pores, harden the skin, stop exudation and light bleeding, effectively covering the wound and preventing the typical bleeding seen in wounds, thereby expediting epithelialization. Steroids possess astringent and antimicrobial properties and exhibit anti-inflammatory and analgesic effects, all contributing to the wound healing process. Saponins stimulate the inflammation phase by stimulating VEGF (Vascular Endothelial Growth Factor) and speeding up the wound healing process. The anti-inflammatory activity prevents prolonged inflammation, thus accelerating the wound healing process [10].

This study is conducted to create an anti-inflammatory gel using catappa leaf extract (*Terminalia catappa*) to enhance wound healing, especially for diabetic patients, and intensify the availability of active ingredients. The choice of gel formulation has advantages, including good drug distribution and release on the skin, good spreadability and adhesion, moisturizing effects without stickiness, water resistance, no residue, ease of use and cleanup. The gel product named GEMAR RIA (GEL ANTIINFLAMASI EKSTRAK Terminalia catappa) is developed utilizing digital advancements, with a barcode on the product's packaging that leads users to an educational website about the product and related diseases.

2. Materials and methods

2.1. Method

This research is true experimental research, through phytochemical, stability tests, antibacterial, and anti-inflammatory. This research was conducted for a month in the Laboratory Chemistry and Bacteriology at Poltekkes Kemenkes Denpasar. In this study, GEMAR RIA was used based on 1 kg of catappa leaves (Terminalia catappa), which obtained from the basketball court of Poltekkes Kemenkes Denpasar. The sample in this study was catappa leaf extract (Terminalia catappa) with a concentration of T1 (25%), T2 (50%), T3 (75%) and diclofenac-natrium as control (Handayani and Pramukantoro, 2020). The percent stability of red blood cell membranes can be calculated by the formula, as follows (Saputra, 2015):

$$\% \text{ Stability of red blood cell membranes} = 100 - \left[\frac{Abs\ test\ solution - Abs\ test\ control\ solution}{Abs\ negative\ test\ control}\right] \times 100\%$$

2.2. Procedure

- ***Sample preparation***

Catappa leaves that have been collected are sorted according to criteria (wet sorting: the raw material to be made dry simplisia must be ensured to be the same species, with a uniform shape, size, color and age, and grow in the same environment in the same area, dry sortation: separate foreign objects or plant parts that are not needed, and to select dry matter to be mashed. The dry material must be completely clean and free from impurities that are still left behind [11]. Then, it was washed with running water until clean, drained, and dried using an oven with a temperature of ± 37 ° C for 48 hours. After ovening, the dried sample is crushed using a blender.

- ***Making Catappa Leaf Extract***

Sample extraction is carried out using the maceration method. Catappa leaf sample powder weighed 250g, then soaked with 70% ethanol solvent with a ratio of 1: 4, stirred and allowed to stand at room temperature for 24 hours. The sample is filtered to produce filtrate, which is inserted into a rotary evaporator with a pressure of 57 rpm at 60° C to produce a viscous extract.

- ***Phytochemical Test***

Flavonoid Identification: A positive result of flavonoids is characterized by the presence of yellow, Alkaloid Identification: A positive result is characterized by the formation of two or three precipitates, Phenol Identification: The result is tested positive if the color of the extract changes to blue-black or purple-black, Tannin Identification: The positive result is characterized by a blackish discoloration, Saponin Identification: The result is tested positive if the foam does not disappear, Steroid Identification and Identification of Steroids and Titerpenoids: Results are tested positive for steroids when a bluish-green ring is formed, while positive for triterpenoids when a brownish ring is formed.

- ***In Vitro Anti-inflammatory Test***

Anti-inflammatory tests begin with manufacturing red blood cell suspensions of mice with 10% concentration (in this study mice were obtained from "Animal and Science Laboratory, Denpasar"), then proceed with manufacturing solutions: test solution, positive control solution, test solution control solution, and negative control solution. After that, proceed with testing with a spectrophotometer Uv-Vis.

- ***Antibacterial Test***

Before conducting antibacterial tests, MHA media and McFarland 0.5 suspense were made, after that, antibacterial tests were carried out with the disc diffusion method.

- ***GEMAR RIA Gel Manufacturing***

The manufacture of Gemar Ria gel preparations is carried out with the following gel formulation.

Table 1: GEMAR RIA gel formulation

Treatment	25%	50%	75%
Extract	1.25 gram	2.5 gram	3.75 gram
Na CMC	0.1 gram	0.1 gram	0.1 gram
Nipagin	0.009 gram	0.009 gram	0.009 gram
Nipasol	0.001 gram	0.001 gram	0.001 gram
Propylene glicol	0.5 gram	0.5 gram	0.5 gram
Aquadest	Ad 5 gram	Ad 5 gram	Ad 5 gram

Na CMC was developed using a small amount of warm aquadest inside the barn. Once the CMC is

homogeneous, it is added with nipagin and nipasol dissolved with 1-2 drops of ethanol. Stirred until homogeneous and then added propylene glycol little by little. Once homogeneous, add the extract according to the formulation made, and the gel mixture is stirred until homogeneous. The empty container is weighed, gel is added and then weighed again. After that, another empty container is weighed, and the aquadest is weighed according to the difference in the mass of the gel by 5 grams. The gel is put back on the mortar and added aquadest that has been weighed gradually and stirred homogeneously. Then the gel can be stored on a prepared container.

2.3. GEMAR RIA Gel Physical Stability Test

Physical stability tests on gels cite methods from [12].

- ***Organoleptic test***

Organoleptic tests evaluate the color, aroma, and texture of Gemar Ria gel preparations observed using the five senses. This test involved 30 volunteers from the Poltekkes environment of the Ministry of Health Denpasar, who were then asked to assess the aroma, color, and texture of the gel on the questionnaire provided.

- ***Spreadability test***

Gel as much as 0.5 grams is placed on a petri dish, then loads weighing 50 grams, 100 grams, and 150 grams on the gel then let stand for 1 minute.

- ***Adhesion test***

The glass object was prepared, then the gel weighed 0.5 grams and placed on the object. Another glass object is placed on top of the gel and given a load of 200 grams for 5 minutes. It was then hung and recorded when both glass objects detached.

- ***Homogeneity test***

The gel is laid out on the glass of the object with 3 different points and then applied. The gel preparation is declared inhomogeneous when there are lumps or coarse grains.

- ***pH test***

The gel is applied to pH paper and then the resulting color is compared to the pH indicator.

3. Results and Discussion

3.1. Phytochemical Test Results

Phytochemical testing was conducted to determine the secondary metabolite content of the catappa leaf extract. The qualitative results of the phytochemical test are presented in the following table.

Table 2: Results of Phytochemical Test

Metabolite Secondary	Results
Flavonoid	(+)
Alkaloid (Wagner)	(-)
Alkaloid (Dragendorff)	(-)
Alkaloid (Mayer)	(-)
Saponin	(+)
Steroid	(-)
Fenol	(+)

From the conducted phytochemical test, it can be observed that the ethanol extract of catappa leaves contains flavonoids, saponins, phenols, and tannins. Saponins are amphipathic glycoside compounds that exhibit the characteristic of foaming. Structurally, saponins consist of lipophilic polycyclic aglycones that can be referred to as sapogenins. Saponins can serve as antioxidants as well as agents for preventing cancer and cholesterol. Saponins can act as antimicrobial agents (sources of antibacterial and antiviral properties), strengthen the immune system, enhance vitality, and also impact collagen (early tissue repair phase) through inhibition.

Compounds such as flavonoids and tannins are substances that can increase the number of fibroblasts in wound healing, thereby facilitating rapid wound recovery[13]. The flavonoid compound of the flavone class has the potential as an antibacterial with potent inhibition against Escherichia coli (gram-negative bacteria) and Bacillus subtilis (gram-positive bacteria) because it has an OH group bound to CH[20]. Different parts of the stem bark, fruit, and leaves of catappa can be used in traditional medicine to treat various illnesses, including childhood skin diseases, dysentery, headaches, and abdominal pain. Research conducted by Behl and Kotwani[14] suggests that Terminalia catappa can offer an effective alternative natural therapy for hyperglycemia and the prevention of diabetes complication development.

3.2. Anti-inflammatory Test Results

Based on measurements conducted with a UV-Vis Spectrophotometer and data processing using predefined formulas, the following results were obtained.

Table 3: In-Vitro Anti-Inflammatory Test Results

Sample	Absorbance Average	%Stability
T1 (25%)	0.0879	99.7
T2 (50%)	0.0519	98.2
T3 (75%)	0.1192	97.1
C (+)	0.1482	97.8

Based on the table above, the test results of anti-inflammatory activity with the cell membrane stabilization method mice red blood based on % stabilization calculations shows that leaf extract Catappa with concentration variations of 25%, 50%, and 75% has anti-inflammatory activity. T1 with an extract concentration of 25% obtained a stability result of 99.7%. On T2 with the extract concentration of 50% obtained a stability result of 98.2%. And at T3 with a concentration 75% extract obtained 97.1% stability result. So, which has the best anti-inflammatory is T1 with the highest stability value of 99.7%.

Catappa leaves contain medicinal compounds such as flavonoids, saponins, tannins, alkaloids, and terpenoids that function as anti-inflammatory agents and can expedite wound healing. The mechanism of action of flavonoids in wound healing involves stimulating the production of endothelial vascular growth factor for the formation of new blood vessels, thereby accelerating wound healing[9]. Anti-inflammatory drugs are a type of medication used to address inflammation caused by disease or injury. Inflammation pain is a medication that can alleviate inflammation caused by non-microorganisms. Anti-inflammatory action is based on the principle of inhibiting the activity of enzymes that trigger the inflammatory process [15]. Synthetic drugs often used as anti-inflammatory agents can sometimes have harmful effects on the body's health. Therefore, it is necessary to seek alternative treatments to combat and control pain and

inflammation with relatively fewer side effects, such as herbal medicines. Wira[16] stated that in the extract of catappa leaves, there are various compound components including flavonoids, alkaloids, saponins, coumarins, tannins, phenolic compounds, and terpenoids that play roles as antioxidants, anticancer, anti-inflammatory, antimicrobial agents, and are capable of suppressing the growth of harmful bacteria. Flavonoids are currently receiving attention due to their potential health benefits. Flavonoids have been reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory, antitumor, and antioxidant effects[16].

3.3. Antibacterial Test Results

Based on the antibacterial testing against the Staphylococcus aureus bacteria strain on Mueller-Hinton Agar (MHA) medium, the inhibitory activity is presented in the following table.

Table 4: Results of Anti-bacterial Test

Sample	Inhibition Average (mm)
T1 (25%)	5.347
T2 (50%)	9.650
T3 (75%)	13.420

From the obtained test results, it can be concluded that the extract of catappa leaves with concentrations of 25%, 50%, and 75% exhibit antibacterial activity against Staphylococcus aureus. According to the classification by Davis and Stout[17], the inhibitory activity of the catappa extract falls into the moderate category, with an interval of 5-10 mm. Then, in the research of Manzur[18] mentioned that T. catappa leaf extract able to inhibit 70% of gram-positive bacteria and 63% of gram-negative bacteria. The catappa leaf extract can prevent the growth of Staphylococcus aureus bacteria. This is attributed to the compounds present in catappa leaves, which have antibacterial or antimicrobial effects. Shedding catappa leaves contain flavonoids and phytochemical compounds called saponins.

Flavonoids are considered as antibacterial agents against pathogenic microorganisms. They work by inhibiting bacterial cell metabolism through the denaturation of bacterial proteins. Phytochemical saponins also possess antibacterial properties. These compounds act as cell membrane disruptors, thereby increasing bacterial cell membrane permeability. During this process, enhanced access facilitates the penetration of antibacterial agents through the bacterial cell wall membrane[19]. On the results antibacterial testing, T3 with an extract concentration of 75% is the best antibacterial Because the diameter formed is the widest.

3.4. Physical Gel Stability Test Results

3.5. Organoleptic Test Results

Based on the organoleptic test conducted on GEMAR RIA, the following results were obtained.

Table 5: Gel Organoleptic Results

Sample	Organoleptic
T1 (25%)	Light brownish in color, without aroma, with a thick gel texture
T2 (50%)	Brownish in color, slightly characteristic, with a gel texture
T3 (75%)	Dark brownish color, characteristic aroma, with a liquid gel texture

An organoleptic test on T1 with an extract concentration of 25% obtained brown color results young, without having an aroma and textured viscous gel. At T2 with an extract concentration 50% obtained a browner, slightly flavorful color, with a slight gel texture liquid. And on T3 with an extract concentration of 75% has the oldest brown color, a distinctive aroma, with a liquid gel texture. The acceptability test involved 30 volunteers consisting of lecturers, students, and campus sanitation personnel from Poltekkes Kemenkes Denpasar. The collected data were then averaged, and the results showed that the most preferred aroma was from the third treatment (T3) with a 75% extract concentration. This was due to its distinct aroma that was not overpowering to the respondents' sense of smell. As for the preferred color, it was T1 with a 25% extract concentration, which exhibited a light brown color. The most favored texture was also observed in T3 (75% extract concentration), characterized by its more liquid texture that easily absorbed.

3.6. Spreadability Test Results

The spreadability test results can be observed in the following table.

Table 6: Gel Spreadability Test Results

Day	25%	50%	75%
Day I	3.7 cm	4.2 cm	5.5 cm
Day II	3.0 cm	3.1 cm	4.8 cm

The gel's dispersion indicates the gel's ability to spread in the area of use. The greater the value of the dispersion diameter illustrates that the gel will spread fast with just a small smear. A good gel is a gel that has the widest dispersion so that the contact between the active substance and the skin-absorbing cells is better [12]. In this experiment, a gel with an extract concentration of 75% had the best dispersion of the gel.

3.7. Adhesion Test Results

Adhesion is a crucial parameter in gel formulation. This test aims to assess the ability of the gel to adhere to the skin. A favorable interpretation of this test involves achieving a high adhesive strength, as a stronger bond between the gel and the skin indicates better drug absorption. The adhesion test was performed twice on the gel formulation, on the first and second days. On the first day, gel concentrations of 25%, 50%, and 75% displayed very strong adhesion between the glass slides carrying the gel and subjected to a 200-gram weight. The adhesion test on the second day yielded similar results, with concentrations of 25%, 50%, and 75% showing strong adhesion that was difficult to detach. This indicates that lower CMC concentrations lead to higher adhesive strength, while higher CMC concentrations result in reduced adhesive strength. Concentration fluctuations lead to interactions between the two bases, depending on the ratio of each substance.

3.8. Homogeneity Test Results

The homogeneity test results for the gel preparations were carried out on the first and second days. The results on the first day showed that the 25%, 50%, and 75% gel concentrations appeared homogeneous, indicated by the absence of rough particles when spread on the glass slide. Meanwhile, the homogeneity test on the second day showed that the 25% and 50% gel concentrations remained homogeneous, while the 75% concentration started to exhibit fine particles when spread.

3.9. pH Test Results

Based on the acidity test of GEMAR RIA using a pH meter, the following results were obtained.

Table 7: pH Gel Results

Day	25%	50%	75%
Day I	4.8	5.1	5.6
Day II	4.79	5.2	5.4

The pH requirement for antiseptic gel preparations that meet the SNI 06-2588 standard is within the range of 4.5-6.5. Antiseptic gel products with very low pH can cause skin irritation, while a very high pH can lead to skin peeling. From the conducted tests, it was found that each treatment from GEMAR RIA met the pH requirements, did not cause irritation, and was safe for human skin.

4. Conclusion and Suggestion

4.1. Conclusion

The most suitable concentration to be used as an anti-inflammatory gel is T3 with 75% Catappa extract. T3 has a high percentage of stability of 97.8% with an antibacterial inhibition zone of 13,420 mm. The physical stability of T3 appears dark brown with a distinct aroma and liquid gel texture. The spreading test T3 on the first day is 5.5 cm and second day is 4.8 cm. The adhesive strength test of T3 on first and second days showing strong adhesive properties. Homogeneity testing of T3 on the first day gels appeared homogeneous, without coarse particles when applied to the glass surface and on the second day test showed that T3 gel began to exhibit fine particles during application. pH testing yielded of T3 on the first day is 5.6 and second day 5.4 (meeting the pH requirements for antiseptic gel formulations set by SNI 06-2588, which fall within the range of 4.5-6.5).

The developed gel product also leveraged digital advancements, incorporating a barcode on the product packaging labeled "GEMAR RIA". This barcode enables users to access a dedicated website providing educational information about the product and related diseases.

4.2. Suggestion

Gel from catappa leaf extract has the potential to be an anti-inflammatory gel for diabetic foot ulcers. However, further research is still needed in vivo test uses experimental animals to determine its effectiveness in the body living things and it is necessary to apply for a BPOM permit to ensure that gemar ria is safe for use in the community.

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