International Journal of Public Health Excellence (IJPHE)
Vol. 1, No. 1, Month 2088, pp. 214~224
Journal Homepage: https://ejournal.ipinternasional.com/index.php/ijphe
ISSN: 2809-9826, DOI: 10.55299/ijphe.v1i2.198

Testing The Effectiveness of Aloe Vera Ethanol Extract Cream on Wound Healing Incision in the Skin of Mice (*Mus Musculus*)

Dilla Sastri Mara
Efarina University, Simalungun, Indonesia

Article Info

Article history:

Received month dd, yyyy
Revised month dd, yyyy
Accepted month dd, yyyy

Corresponding Author:

Dilla Sastri Mara
Efarina University,
Simalungun, Indonesia
Email:
dillasastrimara@gmail.com

ABSTRACT

A wound is an injury to the skin structure of the underlying tissue that may or may not result in a loss of skin integrity. One of the plants used for wound healing is aloe vera (*Aloe vera*). The purpose of this study was to determine the effectiveness and the most effective concentration of aloe vera extract cream for wound healing in mice. This research is experimental research. Because in this study three concentrations of aloe vera extract cream were used 10%, 25%, 50%, and povidone iodine as comparison. From this study, it was found that 10% aloe vera extract cream could heal cuts in mice for 13.2 days. Aloe vera extract cream 25% can heal cuts in mice for 12.6 days. Meanwhile, 50% aloe vera extract cream can heal cuts in mice for 10.6 days. Povidone iodine which was used as a positive control healed cuts on the skin of mice for 12.6 days. The cream base used as a negative control was able to heal cuts in mice for 12.8 days. From this study it can be concluded that the preparation of aloe vera extract cream is effective in healing cuts in mice.

Keywords:

Aloe Vera, Aloe Vera Extract Cream, Cuts, Povidone Iodine.

1. INTRODUCTION

Wounds are physical damage as a result of the opening or destruction of the skin which causes an imbalance in normal skin function and anatomy [16]. Based on the nature of the wound is divided into 2, namely closed wounds and open wounds. Closed wounds are wounds that do not damage the skin tissue, for example fractures and sprains. While open wounds are wounds that cause skin tissue to become damaged or open, damage to the skin can occur intentionally such as surgery, or unintentionally such as accidents. One type of open wound is an incision wound. Incision wound is a condition of a wound with the release of skin tissue in the epidermis, dermis and fascia layers of the body [15].

Wound healing is a complex biological process that results in the restoration of tissue integrity. Physiologically, the wound healing process can be divided into four stages starting from hemostasis, inflammation, proliferation and tissue remodeling. Many factors are known to slow wound healing, namely poor nutrition, hypoxia, immunosuppression, chronic disease and post-surgical conditions. It is very important for surgeons to understand the physiological processes involved in wound healing to minimize patient morbidity from delayed wound healing [29].

As we know, *povidone iodine* is a topical drug that is generally used in wound care and has antiseptic properties, both for gram-positive and gram-negative bacteria. In its use, most of the topical antiseptics more or less interfere with wound healing. Simple cleaning of the wound with soap and water is less damaging than commonly used antiseptic applications. In addition, excessive use of iodine can inhibit the wound granulation process [14].

Indonesia is a country with a tropical climate, this causes the soil to thrive so that many types of plants can grow. Among the various types of plants, some of them have medicinal properties, one of which is aloe vera (*Aloe vera*) [3]. Aloe vera plant is a succulent plant with thick green leaves with white spots on some parts and about 30-50 cm long. This plant is quite easy to find in Indonesia and has been known for several hundred years because of its ability to cure various diseases, besides that aloe vera is also very well known in the world of beauty, especially for skin beauty. The aloe vera plant contains many important components that have medicinal properties, some of which

are glucomans, a fairly high content of polysaccharides and gibberellins (growth hormones) which when interacting with hormone receptors on fibroblasts can stimulate cell proliferation activity and can increase collagen synthesis so that aloe vera plants can used as a wound healing agent [18].

1.1 Aloe Vera (*Aloe vera*)

Aloe vera plant is native to Africa, Ethiopia to be precise and later found in many other dry areas such as certain Asian regions and southern Europe, especially the Mediterranean area. This plant has a botanical name , namely *Aloe barbadensis* Miller [29]. The *Aloe vera plant* also has several names used by local people, such as in France, Portugal, Germany: *Aloe* ; English: *crocodile tongue* ; Malaysian *: jam* ; Chinese *: lu hui* ; Spanish: *sa'villa* ; India: *musabbar* ; Tibetan: *jelly leek* ; Indians: *ailwa* ; Arabic: *sabbar* ; Indonesia: *aloe vera* ; and the Philippines: *natau* .

Nowadays, research on herbal plants that are useful as medicine is rampant. Many herbal plants that have been studied are able to provide a good effect on wound healing, one of which is aloe vera (*Aloe vera*) [17]. A picture of aloe vera can be seen in picture 1 below :

Picture 1 Aloe *Vera*
(Source: kompas.com)

1.1.1 Taxonomy of Aloe *Vera*

Taxonomic levels of *Aloe plants vera* , as follows:
Kingdom : Plantae
Phylum: Spermatophyta
Class : Monocotyledoneae
Order: Liliflorae
Family : Liliceae
Genus : Aloe
Species: Aloe barbadensis Miller

1.1.2 Aloe Vera Morphology

The aloe vera plant is an annual shrub. This annual shrub grows upright, 30-50 cm high. stems round, white, not woody. Single leaf, pointed tip, blunt base, serrated edge, 30-50 cm long, 3-5 cm wide, thick fleshy, yellow gummy, green. Compound flowers, panicle form at the end of the stem, protective leaves 8-15 mm long, six stamens, pistil sticking out or attached to the base of the anthers, pistil stalk in the form of threads, small pistil, the tip of the crown spreading orange or red. The fruit is a box, 14-22 cm long, vegetated, whitish green color. The seeds are small and black. The roots are yellow fibers [5].

1.1.3 Chemical Content of Aloe Vera (*Aloe vera)*

Aloe vera leaves are fat and thick due to their gel-rich content [29]. Aloe vera gel contains 99% polysaccharides (glucomannan) which causes aloe vera leaves to become moist. This gel is part of aloe vera which has many biological and physiological benefits, such as the ability to accelerate the healing of burns and cuts on the skin; prevent wrinkles on the skin; inhibit the growth of bacteria and other microorganisms; increase the body's resistance to the proliferation of cancer cells; and stimulate the body's defense system due to the presence of anthraquinone compounds. *Aloe vera* also contains gibberellins (growth hormones) which, when interacted with growth hormone receptors on fibroblasts, can stimulate cell proliferation activity and increase collagen synthesis.

Several studies have shown that the *Aloe vera plant* has a good antioxidant content. Antioxidants are important substances that protect cells from oxidative damage. Based on phytochemical analysis (qualitative and quantitative) on *Aloe vera leaves*, it was found that almost all chemical compounds used as wound healing agents including antioxidants contained in *Aloe vera leaf gel* , such as tannins, flavonoids (a type of tannin compound), saponins, flavonoids. , steroids, terpenoids and anthraquinone glycosides [24].

Tannins are one type of polyphenolic compound that can be found in both woody and herbaceous plants. Tannin compounds have good biochemical and pharmacological abilities as antioxidants, antitumor, antiviral,

antimicrobial, enzyme inhibitors and free radicals. Tannins are able to precipitate proteins so they are not affected by proteolytic enzymes. Tannins can be used as metal chelators according to the substitution pattern and pH of the phenolic compounds. Tannins make metal chelates more stable and safe for the body, but if used excessively it can cause anemia because iron in the blood will also be chelated [2].

Saponins are glycosides consisting of several sugar groups linked to an aglycone or sapogenin. Saponins have antibacterial and antiviral properties. According to research by Blumert and Liu in 2003 in the third edition of China Immortal Herb, it was revealed that the isolation of sapoinin compounds was efficacious as an anticancer, antitumor and cholesterol-lowering drug.

Flavonoids are the largest phenolic compounds that are widely distributed in nature and based on various researches have been investigated to have pharmacological activity as anti-inflammatory, analgesic and antioxidant. The anti-inflammatory mechanism occurs through the process of inhibiting the arachidonic acid metabolic pathway, the formation of prostaglandins (inflammatory mediators) to the release of histamine in inflammation. Flavonoids can reduce lipid peroxidation by preventing or slowing cell necrosis and increasing vascularity. Flavonoids are also able to increase the viability of collagen fibrils by increasing the strength of collagen fibers.

Steroids are a group of compounds containing a structure with four rings known as a steroid nucleus. Steroids are also very strong anti-inflammatory due to their ability to inhibit phospholipase A2 so that arachidonic acid is not formed. However, because this compound is strong, its use in wound healing must also be appropriate. Based on several studies, this compound can affect fibrogenesis, angiogenesis and wound contraction.

Terpenoids are derivatives of dehydrogenation of terpene compounds and are widely produced by plants and several animal groups. These compounds function to stimulate the formation of extracellular matrix, increase the percentage of collagen in fibronectin cells so that the healing process is faster [14].

1.1.4 Use of Aloe Vera

The use of *Aloe vera* in the field of beauty is generally used in concentrations varying from 1 to 98%. *Aloe vera* has been known as an herbal plant that is able to maintain moisture for a long period of time. Therefore, *Aloe vera* is widely used for skin beauty (cosmetics) as a *moisturizer, cleanser, sun lotions, toothpaste , mouthwashes, shaving creams, deodorants* and *shampoos* .

The use of *Aloe vera* in the food sector, is usually used as food or drink and has been proven to have a good impact not only on topical (external) use but also on systemic (internal) use. In other words, *Aloe vera* is safe for consumption and will actually bring good effects to health. *Aloe vera* can act as a nutritional supplement and also to prevent several diseases. According to research by Serrano et al, *Aloe vera* can also maintain the freshness of food by coating the food, because it can inhibit the growth of microorganisms.

The use of *Aloe vera* as a wound healing drug is due to the presence of polysaccharide compounds and the hormone gibberellin which stimulates increased formation of collagen and elastin. The high healing ability of Aloe vera is influenced by the amount of mucopolysaccharide (MPS) which generally ranges from 10,000 - 20,000 MPS per liter. *Aloe vera* can accelerate wound healing in tissues and prevent the formation of ongoing wounds (chronic wounds) on the skin, this is related to the activity of amino acids in forming new cells and enzymes that initiate regeneration in the deepest layers of the skin.

The use of *Aloe vera* as an anti-inflammatory and antioxidant drug. As an anti-inflammatory , *Aloe vera* contains salicylic acid which acts as an analgesic and anti-inflammatory which can inhibit the production of prostaglandins from arachidonic acid. Meanwhile, as an antioxidant, *Aloe vera* contains many compounds that can eliminate free radicals. According to Lee et al, the activity of *Aloe vera* is similar to *that of -tocopherol* .

The use of *Aloe vera* on skin exposed to UV and X-rays is due to the presence of lectins which have a therapeutic effect. The use of *Aloe vera* on skin and oral mucosal ulcers, herpes simplex and psoriasis. This plant is also known to be able to protect the lining of the stomach (prevent *gastric ulcers*) [7].

1.2 Skin

The skin is the organ of the body that is located at the outermost and limits it from the human environment. The skin area of an adult is 1.5 m² with a weight of approximately 15% of body weight. The skin is an essential and vital organ and is a mirror of health and life. The skin is also very complex, elastic and sensitive, varies with climate, age, sex. race and also depends on the location of the body [7].

As a cover, the skin protects the body from mechanical trauma, radiation, chemicals and infectious germs. Lactic acid in sweat and amino acids resulting from changes in keratinization maintain the pH of the skin surface between 4-6 which will inhibit bacterial growth. However, some types of *streptococci* and *staphylococci* can still live commensurately in the keratin layer, hair estuaries and sebaceous glands [24].

1.2.1 Skin Structure

A. Epidermis Layer

This layer consists of the stratum comeum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale [7].

The stratum komeum (horn layer) is the outermost layer of skin and consists of several layers of dead, non-nucleated flat cells and the protoplasm has turned into keratin (horn substance) [7].

The stratum lucidum, located directly below the coma layer, is a layer of flattened cells without a nucleus with protoplasm that turns into a protein called eleidin. This layer appears more clearly on the palms of the hands and feet [7].

The stratum granulosum (keratohyaline layer) is 2 or 3 layers of flattened cells with coarse-grained cytoplasm and a nucleus in between. These coarse grains consist of keratohyalin. The mucosa usually does not have this layer. Stratum granulosum is also clearly visible on the palms of the hands and feet [7].

Stratum spinosum (stratum Malpighian) or also called *prickle ceil layer* (canta layer) consists of several layers of polygonal-shaped cells that vary in size due to the process of mitosis. The protoplasm is clear because it contains a lot of glycogen and the nucleus is located in the middle. These cells are closer to the surface, the more flattened they are. Between the cells of the stratum spinosum there are *intercellular bridges* consisting of protoplasm and tonofibrils or keratin. The attachments between these bridges form small round thickenings called *Bizzozero nodules* . Between the spinous cells are Langerhans cells. Stratum spinosum cells contain a lot of glycogen [7].

The stratum basale consists of cuboidal (columnar) cells arranged vertically at the dermo-epidermal junction lined up like a fence (*palisade*). This layer is the lowest layer of the epidermis. These basal cells carry out mitosis and function reproductively. This layer consists of two types of cells as follows [7].

1. The cells are columnar in shape with basophilic protoplasm, oval and large nuclei, connected to each other by intercellular bridges.
2. Melanin-forming cells (melanocytes) or *clear cells* are light colored cells, with basophilic cytoplasm and dark nuclei and contain pigment grains (*melanosomes*).

B. Dermis Layer

It is the layer below the epidermis which is much thicker than the epidermis. This layer consists of an elastic layer and a fibrous layer with cellular elements and hair follicles. Broadly speaking, it is divided into two parts as follows [7].

1. *Pars papillare* , the part that protrudes into the epidermis, contains nerve fiber endings and blood vessels.
2. *Pars reticulare* , which is the part below which protrudes towards the subcutaneous, this section consists of supporting fibers such as collagen, clastin and reticulin fibers. The base (matrix) of this layer consists of a thick fluid of hyaluronic acid and chondroitin sulfate, in which fibroblasts are also present. Collagen fibers are formed by fibroblasts, forming bonds (bundles) containing hydroxyproline and hydroxycillin. Young collagen is flexible with age it becomes less soluble so that it becomes more stable. Reticulin is similar to young collagen. Elastic fibers are usually wavy. amorphous and. easy to expand and more elastic.

C. Subcutaneous tissue

Is a continuation of the dermis, consisting of loose connective tissue containing fat cells in it. Fat cells are round and large cells with the nucleus pushed to the edge of the increased fat cytoplasm [7]. These cells form clusters separated from one another by fibrous trabeculae. Layers of fat cells called adipose paniculus, serve as food reserves. In this layer there are peripheral nerve endings, blood vessels and lymph. The thickness of fat tissue is not the same depending on its location. On the abdomen can reach a thickness of 3 cm, in the eyelid area and the penis is very little [7].

Vascularization in the skin is regulated by 2 plexuses, namely the plexus located at the top of the dermis (*superficial plexus*) and those located in the subcutis (*deep plexus*). The plexus in the upper dermis also anastomoses in the papillary dermis, the plexus in the subcutis and in the *pars reticulare* also performs anastomoses, in which the blood vessels are larger. Along with blood vessels there are lymph channels [7].

1.2.2 Skin Function

The skin has various functions to adapt to the environment. The main functions of the skin are as follows [7].

a. Protection function

The skin protects the inside of the body against physical or mechanical disturbances, such as pressure, friction, attraction, chemical disturbances, such as chemical substances, especially irritants, such as lysol, carbolic acid, other strong acids and alkalis, heat disturbances, such as radiation, Ultraviolet rays and interference with external infections, especially germs/bacteria and fungi [7].

b. Absorption function

Healthy skin does not easily absorb water, solutions and solids, but volatile liquids are more easily absorbed, as well as fat-soluble ones. The skin's permeability to O2 , CO2 and water vapor allows the skin to take part in the respiratory function . The absorption ability of the skin is influenced by the thickness of the skin, hydration, moisture, metabolism and the type of vehicle. Absorption can take place through the gaps between cells, through the epidermal cells or through the mouth of the gland duct, but more goes through the epidermal cells than through the gland opening [7].

c. Excretion function

The skin glands secrete substances that are no longer useful or metabolic wastes in the body in the form of NaCl, urea, uric acid and ammonia. Fat glands in the fetus under the influence of androgen hormones from the mother produce sebum to protect the skin against amniotic fluid, at birth it is found as vernix caseosa. The sebum produced protects the skin because this layer of sebum in addition to moisturizing the skin, also prevents excessive water evaporation so that the skin does not become dry. Products of fat and sweat glands in the skin cause skin acidity at a pH of 5-6.5 [7]

d. Perception function

The skin contains sensory nerve endings in the dermis and subcutis. The Ruffini bodies in the dermis and subcutis act on heat stimulation. Against cold are played by Krause bodies located in the dermis. Meissner's tactile bodies are located in the papillary dermis and are responsible for touch, as are Merkel Ranvier bodies located in the epidermis. While the pressure is played by Paccini bodies in the epidermis. These sensory nerves are more numerous in erotic areas [7]

e. Body temperature regulation function (thermogulated)

The skin performs this role by sweating and constricting (contracting muscles) the skin's blood vessels. The skin is rich in blood vessels so that it allows the skin to get good enough nutrition. Vascular tone is influenced by sympathetic nerves (acetylcholine). In infants, the walls of blood vessels are usually not fully formed, resulting in extravasation of fluid, therefore the baby's skin looks more edematous because it contains more water and sodium [7]

1.3 Wound

Wounds are the loss or destruction of part of the body's tissues. This condition can be caused by sharp or blunt trauma, temperature changes, chemicals, explosions, electric shocks, or animal bites. The shape of the wound varies depending on the cause, for example, a cut or *vulnus scissum* is caused by a sharp object, while a stab wound called a *vulnus punctum is* caused by a sharp object. A tear, laceration or *vulnus laceratum* is a wound with uneven or ragged edges caused by an object with an uneven surface. Blisters on the surface of the skin due to friction are called excoriations or *vulnus excorialum* . Heat and chemicals can also cause burns or *vulnus combustio* (Sjamsuhidajat, 2010).

1.4 Wound healing

Wound healing can be divided into three phases, namely the inflammatory, proliferative and remodeling phases [24]

A. Inflammatory phase

The inflammatory phase lasts from the onset of injury until about the fifth day. Broken blood vessels in the wound will cause bleeding and the body tries to stop it by vasoconstriction, constriction of the severed end of the vessel (retraction) and hemostatic reactions. Hemostasis occurs because the platelets that come out of the blood vessels stick together and together with the fibrin mesh that is formed, coagulate the blood that comes out of the blood vessels. Attached platelets will degranulate, releasing chemoattractants that attract inflammatory cells, activate local fibroblasts and endothelial cells and vasoconstrictors. Meanwhile, an inflammatory reaction occurs [24].

After hemostasis, the coagulation process activates the complement cascade. From this cascade, bradykinin and anaphylatoxins C3a and C5a will be released which cause vasodilation and increased vascular permeability resulting in exudation, inflammatory cell pollination, accompanied by local vasodilation that causes edema and swelling. Clinical signs and symptoms of an inflammatory reaction become clear, in the form of a reddish color due to dilated capillaries (rubor), warmth (kaior), pain (dolor), and swelling (tumor) [24].

Cellular activity that occurs, namely the movement of leukocytes through the walls of blood vessels (diapedesis) to the wound due to chemotaxis. Leukocytes secrete hydrolytic enzymes that help digest bacteria and wound debris. Monocytes and lymphocytes that then appear, participate in destroying and eating wound dirt and bacteria (phagocytosis). This phase is also called the sluggish phase because the reaction for the formation of new collagen is small and the wound is only connected by weak fibrin. These monocytes that turn into macrophages also secrete various silokines and growth factors that are needed in the wound healing process [24].

B. Proliferative phase

The proliferative phase is also called the fibroplasia phase, because what stands out is the fibroblast proliferation process. In this phase, collagen fibers are formed and re-destroyed to adjust the tension in the wound which tends to shrink. By the end of this phase, the tensile strength of the wound reaches 25% of normal tissue. Later in the *remodeling process* , the strength of the collagen fibers increases because the intramolecular and anthramolecular bonds are strengthened [24].

C. Remodeling phase

In this phase there is a maturation process consisting of re-absorption of excess tissue, shrinkage in accordance with the force of gravity and finally the re-formation of new tissue. This phase can last for months and is declared

over when all signs of inflammation have disappeared. The body tries to normalize everything that becomes abnormal due to the healing process. Edema and inflammatory cells are absorbed, young cells mature, newly closed capillaries are reabsorbed, excess collagen will be absorbed and the rest will shrink according to the amount of strain [24]

2. METHOD

2.1 Research Design

This type of research is true experimental with a *pre test and post test* research design .

2.2 Research Samples and Sampling Techniques

2.2.1 Research Sample

The sample used in this study was aloe vera (*Aloe vera*) taken from Java Maligas Village, Huta Bayu Raja District

2.2.2 Sampling Technique

The sample taken is aloe vera which is still fresh .

2.3 Research Variables

2.3.1 Variable Type

a. Independent Variable

The independent variable in this study was the variation in the concentration of the ethanol extract cream formula of aloe vera (*Aloe vera*) leaves.

b. Dependent variable

Healing of cuts with indicators of decreasing wound length, and wound closing. Observation time was carried out for 14 days in each group.

2.4 Research Locations And Time

This research will be conducted at the Pharmacy Laboratory of the Faculty of Health, Efarina University starting in July 2021 .

2.5 Research Instruments

2.5.1 Tools

The tools used in this study were a scalpel, scissors, hot plate, glassware, mortar and grinder, ruler, cotton bud.

2.5.2 Material

The materials used in this study were aloe vera, stearic acid, triethanolamine, adeps lanae, liquid paraffin, nipagin, nipasol, aquadest, lidocaine, mice.

2.6 How it Works

2.6.1 Making simplicia

a. Raw material collection

The raw material for simplicia aloe vera (*Aloe vera*). Taken from the Java Maligas Village area. The leaves taken are the leaves that are still fresh .

b. Wet sort

Wet sorting aims to separate foreign materials that are not useful or harmful when making simplicia.

c. Washing

Washing is useful for removing dirt and reducing microorganisms attached to aloe vera (*Aloe vera*).

d. Deformation (slicing)

Deformation is done to expand the surface so that it dries faster without excessive heating.

e. Drying

Drying is done in an open air and should not be exposed to direct sunlight.

f. Dry sort

The purpose of sorting is to separate foreign objects, such as unwanted parts and other impurities that are still present and left behind.

g. Packaging and storage

Aloe vera (*Aloe vera*) can be stored in a dry, not humid, and protected from direct sunlight. Proper packaging and storage can prevent simplicia from fungal contamination.

2.6.2 Extraction of aloe by maceration

In this study, aloe vera extract with 96% ethanol solvent will be used which will be made by maceration technique . The collected aloe vera was then washed, sorted wet and weighed. Aloe vera is dried by aerating to dry and protected from direct sunlight. The dried simplicia were weighed and blended until smooth. Extraction was carried out by maceration by weighing 300 grams of dry aloe which was put into a glass container and then 750 mL of 96% ethanol solvent was added. The simplicia was soaked for 3 days and stirred as often as possible and the

extract was filtered using filter paper and stored in a glass container. Then the remaining simplicia from the immersion was remaceration for 2 days with 250 mL solvent. After all the extracts were obtained, they were then evaporated in a water bath to obtain a thick extract.

2.6.3 Making aloe vera cream

The cream is made with a composition based on the results of previous studies, namely with a cream base that can heal wounds within 14 days.

Table 3.1 Cream Composition

Ingredient	**Heavy**
Stearic acid	14.5 grams
Triethanolamine	1.5mL
Adeps lanea	3 grams
Liquid paraffin	5 mL
Nipagin	0.1 gram
Nipasol	0.05 grams
Aquadest	100 mL

(Farida *et al*, 2011)

a. Weigh all the ingredients needed. The ingredients in the formula are separated into two groups, namely the oil phase and the water phase
b. The oil phase, namely stearic acid, liquid paraffin, adeps lanea was transferred in a porcelain cup, heated on a hot plate at 70 ^{C} until overtime.
c. The aqueous phase, namely triethanolamine and distilled water, was heated on a hot plate at 70ºC until melted.
d. The aqueous phase was slowly added to the oil phase, then added nipasol and nipagin with a stirrer until a homogeneous cream mass was obtained.

To make aloe vera extract cream with a concentration of 10%, 25%, 50%, then the added extract is :

1) Making 10% cream with a weight of 25 grams
   2.5 grams

$$\frac{10}{100} \times 25 =$$

2) Making 25% cream with a weight of 25 grams
   grams

$$\frac{25}{100} \times 25 = 6{,}25$$

3) Making 50% cream with a weight of 25 grams
   grams

$$\frac{50}{100} \times 25 = 12{,}5$$

2.6.4 Test Animals

The test animals that will be used in this study are mice (*Mus nysculus*) which have been adapted to room temperature . The number of test animals was determined using the Faderer formula [2]. Faderer's Formula:

(n-1) x (t-1) 15

Information: n = number of test animals , t = number of treatments

Calculation:

(n-1) x (t-1) 15
(n-1) x (5-1) 15
(n-1) x (4) 15
(n-1) 15/4
(n-1) 3.75
n 3.75 + 1 n = 4.75 (5 samples)

2.6.5 Treatment of test animals

The hair on the back of the mice was shaved with a sterile razor blade, then anesthetized with *lidocaine.* An incision was made on the back using a sterile scalpel 1 cm long. The wound is smeared with cream according to the predetermined concentration 2 times a day. The cream was given from day 1 to day 14. Cuts are treated until they heal, which is indicated by the closing and closing of the wound and a decrease in the length of the wound.

After making the wound, each group was given the following treatment:

a. Group I : Apply aloe vera extract cream with a concentration of

10%
b. Group II : Apply aloe vera extract cream with concentration 25%
c. Group III : Apply aloe vera extract cream with a concentration of 50%
d. Group IV : Apply povidone iodine(K+)
e. Group V : Apply cream base (K-)

2.6.6 Observation parameters

2.6.6.1 Wound healing time

Wounds were observed visually by looking at the condition of the wound and the duration of wound healing ranging from inflamed wounds to dry and closed wounds. The parameters used in this study were to see a decrease in the length of the wound and the duration of wound healing.

2.7 Data Collection Plan

The research data were analyzed using SPSS software version 2 4 . The observed data will be statistically analyzed using the normality test and homogeneity test, followed by the One Way ANOVA test, the difference is declared significant if $p < 0.05$ and followed by a post hoc test to see if there is a significant difference between each treatment. And to see a significant difference between the treatment group and the control group, it was done using the T test.

2.8 Data Analyst

To determine the effectiveness of aloe vera ethanol extract on wound healing in mice, the data were analyzed descriptively by looking at the decrease in wound length and wound closure in cuts. Cuts are said to be healed when the wound is covered by new tissue.

3. RESULTS AND DISCUSSION

3.1 Research Results

3.1.1 Aloe Vera Extraction Results

A total of 300 grams of aloe vera simplicia was extracted by maceration using 96% ethanol as a solvent to obtain 38.27 grams of maserate .

3.1.2 Results of Cuts Healing Test

From the results of research that has been carried out on extracts of aloe vera (*Aloe vera*) for healing cuts on the skin of mice, the results can be seen in table 5.1 below:

Table 2. Average Time (Days) for Healing Cuts in Mice

Mice	Time (Day)				
	PI	PII	PIII	K+	K-
1	13	13	10	13	13
2	13	13	11	13	13
3	12	11	10	12	14
4	14	13	11	12	13
5	14	13	11	13	11
Average	13.2	12.6	10.6	12.6	12.8

Information :
PI = Aloe Vera Extract 10%
PII = Aloe Vera Extract 25%
PIII = 50% aloe vera extract
K+ = Povidone Iodine
K- = Cream dosage base

In table 2, it can be seen that there are differences in the range of time (days) required by each group of mice to completely close their wounds. In the table, it can be seen that mice in the PI group (10% aloe vera extract cream) experienced complete wound closure on the 12th day and no later than the 14th day. Based on the calculation of the average wound healing time, the PI group (10% aloe vera extract cream) needed an average time of 13.2 days. The PII group (25% aloe vera extract cream) showed different results from the PI group (10% aloe vera extract cream), the average time required for the incision to close completely was 12.6 days. In the PIII group (50% aloe vera extract cream), some mice recovered on the 10th day while the other 3 mice recovered on the 11th day. The group took an average of 10.6 days. In the positive control treatment group, it took an average of 12.6 days. Meanwhile, in the negative control group, it took an average of 12.8 days.

3.1.3 Results of Data Analysis

a . Normality test

Table 3 Normality Test Results

Tests of Normality

		Kolmogorov-Smirnov [a]			Shapiro-Wilk		
	group of mice	Statistics	df	Sig.	Statistics	df	Sig.
Weight	PI	.165	5	.200 *	.988	5	.973
	PII	.228	5	.200 *	.951	5	.748
	PIII	.177	5	.200*	.957	5	.788
	Kontrol positif	.236	5	.200*	.895	5	.382
	Kontrol negatif	.197	5	.200*	.929	5	.590

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

The amount of data taken is less than 30, the table used is p from the Shapiro-Wilk table by looking at the value of Sig. which is obtained. The results of the normality test for wound healing in mice showed that the Sig value of the PI group (p=0, 973), the PII group (p=0.7 48), the PIII group (p= 0.788), the positive control group (p= 0, 382), and the control group was negative (p= 0,590) where P>0,05 so it could be concluded that the data were normally distributed.

a. Homogeneity Test

Table 4 Homogeneity Test Results

Test of Homogeneity of Variances

Weight

Levene Statistics	df1	df2	Sig.
1.126	4	20	.372

data above shows p> 0.05 (Sig. 0.372) which means that the treatment and control groups are homogeneous.

b. Anova Test

Table 5 ANOVA . Test Results

ANOVA

TOTAL

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	9,427	4	2,357	8,246	,000
Within Groups	5,716	20	,286		
Total	15,143	24			

The ANOVA results can be seen from the ANOVA table column Sig. It can be seen that p = 0.000 means that there is a difference in the average reduction in wound length between all treatment groups.

c. Post Hoc Test

Table 6 Post Hoc Test Results

Multiple Comparison

Dependent Variable: TOTAL

Bonferroni

(I) Group of mice	(J) Group of mice	Mean Difference (IJ)	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
PI	PII	,42400	,33812	.001	-,6422	1.4902
	PIII	1.70400 *	,33812	.001	,6378	2.7702
	positive control	,34400	,33812	,002	-,7222	1.4102
	Negative control	,10400	,33812	.001	-,9622	1.1702
PII	PI	-,42400	,33812	.001	-1,4902	,6422
	PIII	1.28000 *	,33812	,0 0 1	,2138	2.3462
	positive control	-.08000	,33812	,00 4	-1.1462	,9862
	Negative control	-,32000	,33812	,003	-1.3862	,7462
PIII	PI	-1.70400 *	,33812	.001	-2.7702	-,6378
	PII	-1.28000 *	,33812	,0 0 1	-2.3462	-,2138
	positive control	-1.36000 *	,33812	,007	-2.4262	-,2938
	Negative control	-1.60000 *	,33812	.001	-2.6662	-,5338

*. The mean difference is significant at the 0.05 level.

It can be seen in the data above that each treatment (PI , PII, PIII, K +, K-) obtained a P value <0.05 which means that there is a significant difference between each treatment group in the healing time of cuts in mice.

3.2 Discussion

In this study, the test of the effectiveness of wound healing was based on decreasing the length of the incision. On the day of treatment, the scalpel was scratched on the back skin of the mice which had been shaved and anesthetized using lidocaine cream, then scratched to form a 1 cm long cut. When the wound is formed, bleeding is seen due to damaged or cut blood vessels, this is possible because it affects the blood vessels in the *papillary pars* (the part of the dermis that protrudes into the epidermis). In accordance with the theory according to [7] that in the dermis layer there is *papillary pars* which is the part that protrudes into the epidermis, contains nerve fibers and blood vessels. The bleeding does not last long because of the body's physiological mechanism to stop the bleeding. This is in accordance with the theory put forward by [24] that after the occurrence of bleeding the platelets will come out of the blood vessels and together with the fibrin mesh will stick together to form blood clots.

The macroscopic picture that was seen after the incision was made on the back of the mice was redness and swelling at the edge of the wound, besides that the mice were trying to scratch and bite the area of the cut. This description explains the theory put forward by [24] that the wound experiences an inflammatory reaction which is marked by a reddish color (rubor) because the capillaries are dilated and swelling (tumor) occurs.

From the data above, it can be seen that aloe vera extract cream can heal cuts in mice with a length of 1 cm. This happens because aloe vera contains polysaccharides that can speed up the wound healing process and reduce the inflammatory reaction. In addition, aloe vera also contains saponins that can kill germs.

Each mouse was given a different concentration of 10%, 25% and 50%. Of the three concentrations of aloe vera cream given, mice with a concentration of 50% were the fastest recovering mice, with an average of 10.6 days. This happened because the 50% aloe vera extract cream contained more aloe vera extract compared to the 10% and 25% concentrations.

Mice treated with povidone iodine recovered in less than 14 days. In practice, povidone iodine has been clinically tested as an antiseptic and has been used for a long time in medical practice. Povidone iodine has antiseptic properties, both gram positive and negative bacteria so that it can minimize pathogenic bacteria that can inhibit wound healing [14]. Based on this theory, the therapeutic effect of povidone iodine as an antiseptic can help the healing process of cuts in mice with an average time of 12.6 days. Mice given the cream base also recovered in less than 14 days. This is because the basic ingredients of the cream contain adeps lanea which can increase absorption so that the wound dries faster and does not rot .

4. CONCLUSION

The preparation of aloe vera ethanol extract cream was effective in the healing process of cuts on the skin of mice. The most effective preparation of aloe vera ethanol extract cream for wound healing on the skin of mice was a concentration of 50%. Wounds heal within 10 days.

ACKNOWLEDGEMENTS

Author thanks you to all who were involved in writing this article, hopefully it will be useful for all readers wherever they are.

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