

Pathophysiological and Antibacterial Effects of Aloe Vera Gel Extract on Staphylococcus Aureus-Infected Wounds in a Murine Model

Fatima M. Bader^{1*}, Kawakib I. Al-zubaidy¹

¹ Department of Biology- Qurna Education Collage \ University of Basrah, Iraq

ABSTRACT

Background: Aloe Vera has been traditionally used for its therapeutic properties in treating various skin conditions. This study investigates the histopathological effects and antibacterial properties of alcoholic Aloe Vera gel extract on wounds infected with *Staphylococcus aureus* in a murine model. **Methods:** Thirty-two mice were divided into four groups: a treatment group infected with *S. aureus* and treated with alcoholic Aloe Vera gel extract, a positive control group infected with *S. aureus* only, a negative control group with only the wound, and a healthy control group. The effectiveness of Aloe Vera was assessed through histopathological examination and measurement of wound diameters at various stages of the healing process. **Results:** The treated group showed significant inhibition of *S. aureus* and accelerated wound healing compared to controls. At day four, wound diameters were significantly smaller in the treated group (9.000 mm) compared to the positive (12.500 mm) and negative controls (11.000 mm). This trend continued, with the treated group showing a wound diameter of 3.500 mm at day twenty-one, compared to 5.500 mm and 4.500 mm in the positive and negative controls, respectively. Histopathological analysis revealed enhanced repair processes in the treated group, characterized by the early appearance of granulation tissue and a more rapid resolution of inflammation. The positive control sections displayed persistent inflammatory cells and slower repair kinetics, while the negative control showed delayed formation of skin layers. **Conclusion:** The alcoholic extract of Aloe Vera gel significantly modulates the pathophysiological response to *S. aureus* infection in wounds, demonstrating potent antibacterial and wound-healing properties. These findings suggest that Aloe Vera could be a valuable agent in enhancing skin repair mechanisms, with implications for both clinical and pathophysiological applications in wound management.

Keywords: Aloe Vera Gel, *Staphylococcus Aureus*, Wound Healing, Histopathology

INTRODUCTION

Wounds represent a serious health problem that is often overlooked, especially if left untreated, as they show many complications, including infection, blood poisoning, amputation [1], where many patients suffer from them, especially those in hospitals, which start from simple inflammatory cases to those that cause serious complications, and these bacterial infections that affect the skin such as boils, hair folliculitis, infectious herpes, It has also been noted in recent years that hospital-related infections have increased significantly caused by antibiotic-resistant polycoccal strains [2]. There are many microorganisms that naturally live on the skin such as *Staphylococci*, *Brevibacterium*, *Streptococci*, *Corynebacterium* as well as *Candida*, when the skin is infected with one of the injuries such as burns, ulcers, scratches, trauma, wounds and others, it will lead to the penetration of the skin's defense, allowing bacterial invasion of the skin, causing mild to serious skin infections [3] as most wound infections are caused by a bacterial invasion that may be caused by bacteria naturally coexisting on human skin, such as *Staphylococcus epidermidis*, Which is become pathogenic when they enter to wound then to circulatory system [4, 5], the most common diseases caused by bacteria in the skin are Boils, cellulitis, impetigo, folliculitis, acne vulgaris. Most of the infected skin wounds are contaminated with bacteria from the surrounding environment, i.e. microbiota bacteria that are naturally present on the skin, and it was found that the positive bacteria, especially *Staphylococcus aureus*, are at the forefront of bacterial species that cause various skin injuries, followed by negative bacteria such as *coli Escherichia* and *Pseudomonas sp*, which were discovered to invade deep layers, causing damage to skin cells

significantly [6]. the multi- drug resistant bacteria are the ones that affect skin burns [7]. Studies have also shown that *Staphylococcus aureus* is most common in young people with skin injuries [8]. Infection with *Staphylococcus* is a major problem because of its resistance to antibiotics, especially Methicillin-resistant *Staphylococcus aureus* (MRSA) they are more pathogenic and fatal compared to Methicillin-sensitive *Staphylococcus aureus* (MSSA) [9, 10], *Pseudomonas aeruginosa* is one of the most important pathogenic bacteria that can germ blood (bacteremia) and infect wounds [11], which is responsible for 70% of deaths in burn patients [12], in addition to species such as *Streptococcus pyogenes*, which are considered pathogenic bacteria [13] as well as *Acinetobacter spp*, non-coagulant *Staphylococcus* and coagulase-negative *Staphylococci* such as *Staphylococcus epidermidis* and *Staphylococcus lugdunensis* [14], as the wound is infected at the beginning with *Staphylococcus*, which usually grow at pH 7, while the bacteria that infect the wound recently after it becomes more acidic are *P. aeruginosa*, *Enterococcus faecalis* where they can live with a wider pH, while *Peptostreptococci* are present in more alkaline wounds [15]. Aloe Vera was found to be effective in treating skin injuries and promoting the healing process such as burns, bruises, skin infections, surgical wounds, infections, herpes ulcers, diabetic foot ulcers, external pressure ulcers and chronic wounds [16] due to the presence of mannose-6-phosphate found in the gummy gel of the aloe Vera plant, as it is the active ingredient for wound healing [17]. In addition, other studies have shown that the wound healing process is due to the presence of pectin-like Rhamnogalacturonan and acemannan, which improves skin [18].

MATERIALS AND METHODS

Extraction

1. Aqueous extraction: The aqueous extracts [19] were prepared by taking 370 grams of freshly gel aloe leaves with 100 ml of distilled water and crushing them in a blender, stirring them in a vibrating incubator for 12 hours, filtering them through Whatman No. 1 filter paper and then drying them, where approximately 1.2% is obtained. The dry powder is then stored in opaque, airtight containers in the refrigerator at -20°C for later use.

2. Alcoholic extraction: The alcoholic extract was prepared following the steps mentioned by Halima et al. [20]. 1. Fresh mature leaves of plant with length (30-25) cm were cleansed in tap water for 5 minutes then washed with sterile distilled water, after that sterilized with 70% ethyl alcohol and the leaves were left upside down for 15-30 minutes to allow the liquid yellow substance in the leaves to descend for disposal. 2. By a sterile knife, the leaves were separated longitudinally and the inner gel of the leaf was taken and dried in sterile environmental conditions at a temperature of 25 °C to preserve it from contamination or damage. 3. Desiccant gels are crushed to obtain powder using mortar or electric grinder. 4. Soak 10 g of this powder in 100 ml of absolute ethanol for 4 days to properly extract the active compounds at 25 degrees and in opaque bottles, the extract was later filtered by Whatman No. 1 and sterile papers 0.22 with a vacuum pump to be taken for freezing and kept in the refrigerator at 4°C until use.

Characterization of the Extract according to Colorimetric Tests

1. Molisch test: A test used to detect sugars in general that produce furfural compounds when they react with concentrated sulfuric acid. two drops of alpha naphthol alcohol are added to 2 ml of the sugar solution in a test tube, the mixture is shaken well, then added 1 ml of concentrated acid carefully on the inner walls of the tube, forming two layers representing the sugar solution for the top and the acid for the bottom, and at the separating surface, the violet ring appears. Indication On the positive interaction.

2. Benedict test: Use to detect reducing sugars by adding 2 ml of the reagent consisting of copper sulfate, sodium citrate and anhydrous sodium carbonate to 1 ml of the sugar solution with the tube placed in a boiling water bath for 5 minutes, where a red precipitate of copper oxide is indication of a positive reaction.

3. Biuret test: This test was used to detect proteins in plant extracts by adding 0.5 ml of aqueous copper sulfate solution at a concentration of 1% to 1 ml of plant extract and shaking well, then two drops of 40% NaOH solution were added and shake well.

Laboratory Animals

Male white *Mus musculus* L. of the BALB / C strain at the age of 10-12 weeks and weight ranging between 20-25 g were used, as it was brought from the Department of Biology / College of Education at Tikrit University / Iraq and was housed in the animal house of the Department of Biology at the College of Education / Qurna - University of Basra / Iraq under controlled and similar conditions of temperature 20-25 °C and a stable lighting system of 12 hours of light and 12 hours of darkness and good ventilation [21]. Mice were placed in plastic cages with dimensions (20×30×10 cm) brushed with wooden sawdust to be replaced every two days.

Experimental Design

Experimental animals were treated in accordance with internationally agreed animal welfare ethics stipulated by animal welfare societies according to the federal Animal Welfare Act (AWA), animals used in experiments must have adequate housing, treatment, veterinary care, food and water, the experiment of the current study includes (32) mice distributed in single plastic cages where there was a cage for each mouse with dimensions (12×12×10 cm), as they were sterilized with 70% ethanol alcohol and brushed with sterile wooden sawdust, replaced daily throughout the experiment period to ensure that there is no contamination to the animals with microorganisms throughout the trial period. Mice were divided into four groups, each group consists of (8) mice and as follows: 1. the treated group: Skin wounds contaminated with *S. aureus* were infused with alcoholic aloe Vera extract. 2. positive control (C1) The latest wound in the skin contaminated with *S. aureus* only. 3. negative control (C2): induced wound on the skin only. 4. Control group (C3): Healthy animals.

Estimating of Infections Dose (ID50) to *Staphylococcus Aureus*

It was performed in vitro according to the Miles & Misera [22] method where the unit of colony formation (colony forming unit) was calculated according to the following formula:

$$\text{CFU/1ml} = \text{Average of colony} \times 50 \times \text{dilution factor}$$

The reason for choosing a murine model, a preliminary experiment was conducted to evaluate the effectiveness of the extract as an antibacterial on a number of pathogenic bacterial isolates, where *Staphylococcus aureus* was the most sensitive species to the extract. It is one of the most common causes of skin infections, so this type of bacterial infection was chosen. In addition, the skin represents one of the natural immune barriers as it covers the entire body and protects it from pollutants and external influences, and therefore exposure to wounds or diseases poses a great danger to the health of the entire body.

Method of Inducing a Wound

Mice were anesthetized by inhalation the chloroform about 5-10 minutes, as the animal became unable to move for a certain period, which helped to cause a longitudinal wound with a length of 1-1.5 cm in the animal's torso by disposable sharp surgical blades and a full depth of all skin layers to ensure that the animals are exposed to the same wounds and effect, taking into account ethics of dealing with animals, as the animal was completely sterilized by iodine disinfectant after shaving the dorsal area of the animal completely by electric shaver, wounds of the mice in treated group and the second control group were then contaminated with *Staphylococcus aureus* by disposable cotton swab.

Treatment Method

Mice in treated group exposed to a wound contaminated with bacteria was treated with the extract of 0.25 g plus 1 g of vaseline after 4 hours of the wound events twice-daily for a period of 21 days [23].

Histopathological Study

Experiment was included four periods (4, 7, 14, 21) days, random animals were taken from each group at each period and drugged with general anesthesia with chloroform, where they were dissected and skin samples were preserved in the stabilization solution, after which the paraffin sections were stained by eosin and

hematoxylin dye and examined with a microscopy under a magnification force of 40X.

Results

Extraction

1- Aqueous extraction: Depending on Wabeya et al [19] method in Aqueous extraction, was obtained 0.2 g of every 100 g of fresh aloe Vera gel. 2- Alcoholic extraction: According to the method used, which is what was stated by Halima et al. [20], 0.1 g of every 100 g of fresh aloe Vera gel was obtained after extraction.

Characterization of Active Compounds in Extracts

1. Molisch test: The results of the test showed the appearance of the purple ring, which is indication of the positive reaction and the presence of polysaccharides as in Figure (1).

2. Benedict test: The results of the test showed the formation of a red precipitate of copper oxide indication of positive reaction and the presence of reducing sugars, as in Figure (1).

3. Biuret test: The absence of color change in the reagent (Biuret reagent) when added to the extract is evidence of negative reaction and the absence of proteins as in Figure (1).

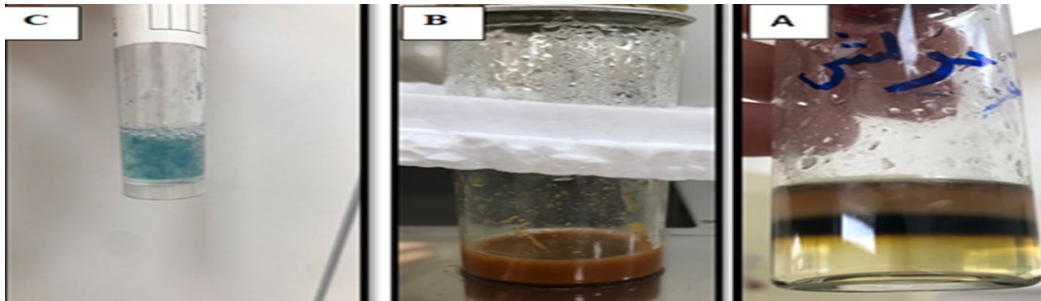


Figure 1: Colorimetric Tests

Measuring the Wound Lengths in Laboratory Animals

The rates of wound lengths for animal groups during the experimental periods showed a healing of skin wounds in the group of animals treated with aloe Vera alcoholic gel extract faster and better

during the first days of the experiment starting from the fourth day compared to other control groups (The wound group treated with bacteria only and the wound group only) at a rate of 6.250 mm by measuring it by a measurement ruler in millimeters as shown in Figure (2).

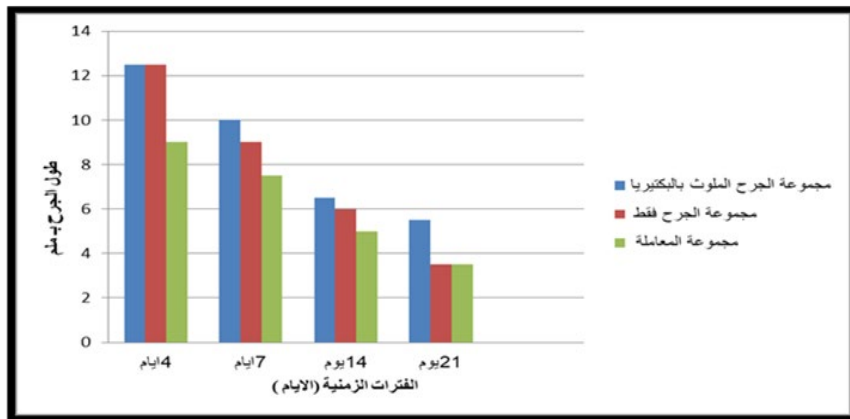


Figure 2: A Verage of Wound Lengths

Histopathological Study

The results of the study of the skin tissue sections of the experimental animals during the successive periods (4, 7, 14 and 21) days showed that on the fourth day of the experiment, the skin tissues of the treatment group wounds showed the formation of soft clot and thick epidermal layer as well as granulation tissue. Histological examination of the positive control group showed signs of necrosis as well as the spread of inflammatory cells in the tissue around the wound. As for the histological examination of the negative control group, it was clearly observed that the cut in the epidermis area includes the removal of all its layers, and the area around the wound appears free of inflammation cells and dead cells, with small clots above the wound, in addition to that, the area of the dermis under the wound has changed significantly, as the hair follicles and sweat glands also disappeared. It was found that the longitudinal tissue sections that

pass in the center of the wound for the treatment group after seven days of the experiment, showed the presence of a thick blood clot at the top of the wound area with a decrease in the density of granulation tissue in the wound area at the expense of skin tissue (epidermis and dermis), as it was observed that thick epidermal layer is formed in the wound area with condensation of thick collagen fibers in the dermis area, and the wound area without appendence of skin, as well as the longitudinal sections that passed through the edges of the wound for the same group and in the same period, it was clearly shown that the repair of the epidermal tissue and renewed skin cells with clarity of the epidermal layers and condensation in the connective tissue of the dermis layer with no skin appendence. Unlike the longitudinal sections of tissue taken from positive control wounds, it showed that the wound area keeps the same specifications as it was in a period of -4- days, noting the beginning of the appearance of granulation tissue in the deep part

of the wound and the large spread of inflammatory cells as well as condensation of collagen fiber bundles of connective tissue in the dermis layer in addition to the lack of complete formation of the epidermis layer. Clot with the beginning of the formation of the epidermis layer on both sides of the center of the wound as well as the densification of the connective tissue in the dermis and the absence of skin appendence that are located on both sides of the wound area. After 14 days of experiment, longitudinal histological sections of the wound treatment group, peeling of the blood clot that was covering the wound in -7- days with increasing the thickness of the epidermis layer and completion of its repair, as well as thickening of connective tissue in the area of the dermis devoid of skin extensions, in addition, the wound area appears slightly low or at the level of the surrounding areas. Histological sections of positive control wounds showed the presence of a blood clot in the upper part of the wound with the onset of healing of the epidermis layer and thickening of connective tissue in the dermis with the level of the wound area lower than its surroundings in healthy tissue. While the histological sections of the control wounds showed that the formation of scar tissue includes the presence of the epidermis layer in a thick form, where the skin lack. In the longitudinal

histological sections of the skin wounds in the treatment group after 21 days of experiment, the complete removal of scarring tissue and restoration of the natural shape of the tissue in the epidermis and dermis layers with the restoration of normal architecture including hair follicles and other skin extensions so that it is difficult to distinguish the wound area from the surrounding areas of healthy tissue. While a delay was observed for repairs in positive control wounds equivalent to 7 days compared to the other two groups (treatment and negative control), and the lack of return of the normal composition of the skin tissues, due to the thickening of the epidermis layer and collagen fiber bundles in the dermis layer, as well as the height of the wound area from the surrounding areas of healthy tissue, with the loss of skin extensions from glands and hair follicles. The histological sections of the negative control wounds when compared with the treated group, showed that the repair operations that took place in this group were not accompanied by a complete return to the normal composition, as the epidermis layer in the wound area is still thicker in the areas around it, in addition to the collagen fiber bundles in the dermis layer, as well as being free of skin extensions from hair follicles and glands as in Figure (3).

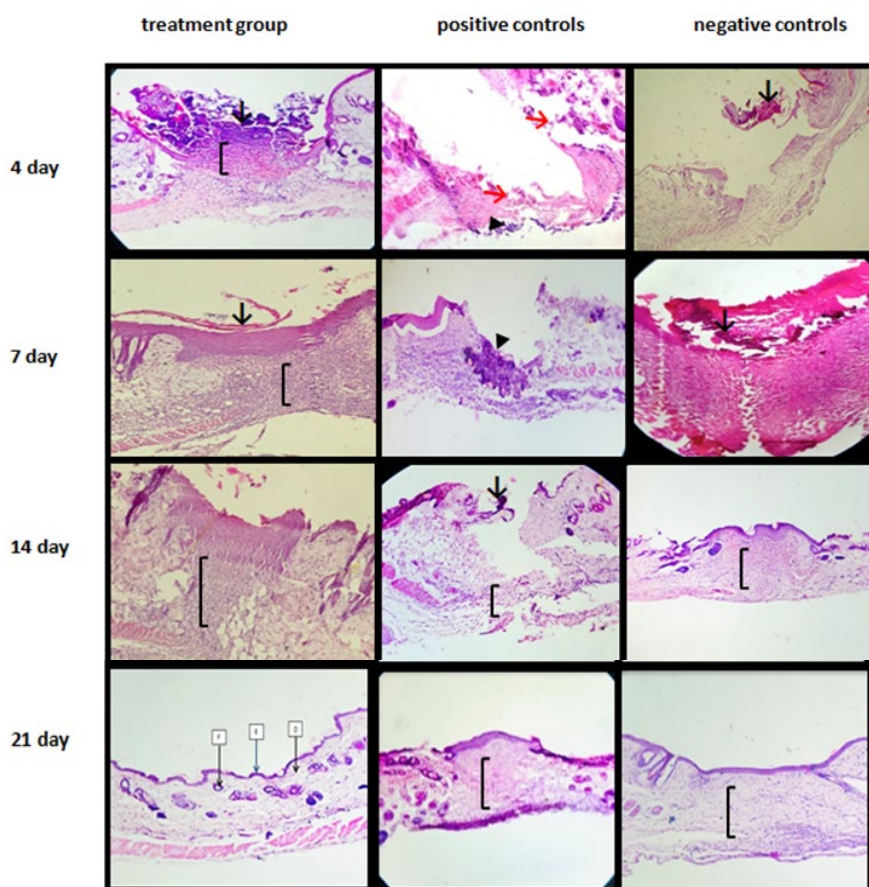


FIGURE 3: Longitudinal Sections of Wound Healing Stages in the Skin of Mice During the Experiment Period, Clot (Black Arrow), Granulation Tissue (Black Arch), Tissue Necrosis (Red Arrow), Inflammatory Cells (Arrowhead), Epidermal Layer (E), Dermis (D), Follicles (F). H. &E. (X40).

Discussion

Colorimetric Methods

The appearance of the purple ring in the molch reaction of sugars is based on the interaction of concentrated sulfuric acid with pentose sugar and hexagonal sugar, which removes some water molecules,

producing furfural from pentose sugar and hydroxyl methyl furfural from hexagonal sugar, and each of them can interact with alpha-naphthal, forming a red-violet compound that appears as a ring between the two separation surfaces that express the positive reaction. As for the Benedict test, its positive result is due to the oxidation of reducing sugars by copper ions, producing a carboxylic acid, and red copper oxide is formed, where it appears in the form of a red or orange

precipitate (positive reaction evidence), i.e. the presence of mono- and reducing sugars. While the biuret reaction showed no color change to the reagent and this is evidence of the absence of proteins.

Histopathological Study

Wound healing in laboratory mice was followed up over 21 days and at certain time intervals by studying the histological changes that occurred in the skin wounds of mice of the groups studied in the present experiment. Where the longitudinal sections of the tissue were examined to know the role of bacteria in tissue damage and delay the wound healing, as well as evaluating the effectiveness of aloe Vera gel in eliminating these bacteria and accelerating the healing process. Skin wounds were in the group that infected with bacteria and treated with the Aloe Vera gel extract topically has a clear and remarkable progress in healing compared to control groups (group of wounds treated with bacteria only) where the histological sections of the wounds of the treatment group on the fourth day of the experiment showed signs of repair in the wound area, which was represented by blood clot, which is the first mechanism of the healing process after the wound occurs, which works to prevent blood flow and continued bleeding as well as preventing the entry of bacteria into the wound, and also showed condensation of the newly formed epidermal layer, which indicates increased epithelial cell reproduction and the construction of new cells. In addition to the condensation of granulation tissue in the wound area, which is Fibrous connective tissue grows from the base of the wound to replace the blood clot in the healing process, which showed the effectiveness of the extract in inhibiting bacteria contaminating the wound and its medical effectiveness in stimulating the wound healing and the formation of skin layers when used topically in treatment, and this is consistent with a study conducted by Adnan et al. [24], which showed the effectiveness of aloe Vera gel in treating burns of the skin of rabbits infected with *Staphylococcus aureus* bacteria by eliminating bacteria in addition to accelerating the wound healing, compared to the control groups, which are the positive control group (wounds infected with bacteria only) who did not show any of the signs of repair mentioned as well as the presence of evidence of tissue necrosis by bacteria and the spread of inflammatory cells in the tissue around the wound as a result of the presence of bacteria, while negative control group (wound only without treatment) It did not show any sign of repair except a small blood clot, in addition to that it did not show signs of inflammation and dead cells, and the cause may be due to wound events under sterile conditions represented by the use of sterile single-use sterile tools and blades, which did not cause any case of bacterial contamination in the wound. When following the stages of group healing on the seventh day of the experiment, the apparent changes in the longitudinal sections of the center of the wounds of the treated group indicated a clear progress in the healing stages compared to the fourth day, as these signs were the presence of a thick blood clot, increased skin thickness, decreased granulation tissue and thickening of collagen fibers, which may indicate stimulation of the extract to increase the effectiveness of fibroblast-generating cells, moreover the operations of complete repair in the longitudinal sections of the wound extremities for the same period except for the absence of skin appendage, and this can be due to the fact that one of the mechanisms of aloe Vera gel in the wound healing process is to reduce inflammation in the wound area in addition to other mechanisms such as increasing collagen and cell migration as well

as maintaining the moisture of the wound area [25, 26] as well as one of potential mechanisms underlying the antibacterial effects of Aloe Vera gel extract it contains active compounds that act directly as anti-bacterial such as saponins, anthraquinones, tannins, aloin and acemannan [27]. These mechanisms may be due to the presence of Tannic acid in addition to the presence of multiple sugars that contribute to the wound healing and tissue repair, as the gel contains multiple sugar Glucomannan rich in mannose sugar and gibberellin growth hormone, both of which work to stimulate fibroblasts and increase their proliferation through their binding to growth factor receptors on the surfaces of these cells [28], and this is consistent with the findings of [29], who confirmed the effectiveness of aloe Vera in treating wounds contaminated with *Staphylococcus aureus* as an antidote to these bacteria and contribute to wound healing by increasing collagen formation in the wound area of dog skin, it was found that the polysaccharides in aloe Vera gel work as antibacteria against both negative and positive bacteria [30] and these sugars include Acemannan, which is the main component of carbohydrates, which helps stimulate wound healing and regeneration of skin tissue by stimulating collagen synthesis and stimulating the growth factor of the lining of blood vessels, and it was also found that it works to prevent the adhesion of *Pseudomonas aeruginosa* from adhering to the epithelial cells of the lung [31, 32], as well as the high glucose content in aloe Vera prevents bacteria from growing as a result of osmotic virtue, in addition to the presence of saponins and anthraquinones in the gels that are effective in inhibiting bacteria [33]. The positive control group had more inflammatory cells than on the fourth day as an indication of the effect of bacteria on the occurrence of tissue inflammation and delayed the healing process, while the negative control group showed the onset of healing that appeared on the fourth day in the treatment group. At the fourteenth day of the experiment, it was found in the longitudinal sections of the wounds of the treatment group in which the skin is very thick evidence of the speed of the healing and the formation of cells quickly with the density of connective tissue and the completion of repair operations in the wound area and the formation of tissue, but it is devoid of skin extensions, and the appearance of the wound area at a slightly low level or equal to the level of healthy tissue around it may give an indication that the healing occurred correctly without the presence of tissue. scar, because the abundant gel contains aloctin-A, which has an effective effect on cell division of living cells, accelerating the healing and stimulating phagocytes to get rid of dead tissue [34], While the positive control group was at the beginning of the healing stages due to the presence of a blood clot and the beginnings of healing of the epidermis layer. Appearance of granulation connective tissue with a significant decrease in the wound area from the surrounding healthy areas and this indicates a clear delay in the tissue repair, as for the negative control group, the healing processes were characterized by thickening, i.e. an increase in cell production with the height of the wound area from what is around it from healthy skin, which is an indication of the formation of scar tissue that distinguishes the wound area from the surrounding areas. At the twenty-first day, the longitudinal sections of the wounds of the treatment group showed the return of the natural structure of the skin, as well as the formation of a number of hair vesicles in the area to a degree that is difficult to distinguish from the surrounding healthy skin, and this is evidence of the speed of the healing process and stimulating the

formation of hair follicles by the extract, which may be due to the presence of mannose sugar in the aloe Vera gel, which is one of the factors helping to heal wounds, as it helps to increase the activity of phagocytes, which have a role in eliminating bacteria as well as it works to promote wound healing by increasing the speed of proliferation of fibroblasts responsible for collagen production. Mannose 6-phosphate in aloe Vera gel participates in wound healing either directly or indirectly by stimulating collagen, as collagen is a necessary factor for the formation of fibers in the wound area as well as repairing it through protein synthesis and increasing enzymatic effectiveness. Aloe Vera helps enhance oxygen levels in the wound and thus improve the blood circulation in the vessels micro-which helps the migration of epithelial cells that are involved in the healing. This is consistent with the findings of [35] where they proved the effectiveness of aloe Vera gel in treating donkey list wounds when applied topically to the wound. Unlike the tissue sections of the positive control group, in which the repair operations were late from the treatment group and the negative control group only by 7 days, and the lack of return of the normal structure of the skin and the absence of skin appendence in the area, as well as the

height of the wound area from the surrounding healthy areas characterized by scar tissue, as the sections of the negative control wounds group for the same period showed condensation of the skin layers and their absence of accessories from glands and hair follicles indicating the completeness of the repair stages in them, and these.

In control groups, the advantages of using aloe Vera gel in eliminating bacteria and treating wounds without leaving scars, that is, not leaving traces of wounds on the skin in the future, were evident. It agrees with a study [36] that showed that aloe Vera gel is more effective in treating staphylococcus-contaminated skin wounds compared to the antibiotic gentamicin.

Conclusion

It is concluded from this study that aloe Vera gel has great effectiveness in eliminating bacteria contaminating skin wounds and helping to speed up healing and restore the skin to its natural shape without leaving any trace on the skin, as well as stimulating the hair follicle growth, so it can be used in treating other skin diseases such as Boils, cellulitis, impetigo, folliculitis, acne vulgaris.

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