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Assessing the Therapeutic Potential of Arctium lappa L. (Burdock Root) Ethanol Extract in Wound Healing on Male Rattus norvegicus

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Abstract: Burdock root (*Arctium lappa L.*) is known for its rich content of lignans, flavonoids, and phenolic acids, which exhibit anti-inflammatory, antioxidant, anti-cancer, and free radical-scavenging properties, making it a promising agent for wound healing. This study aims to evaluate the efficacy of *Arctium lappa L.* ethanol extract in promoting wound healing in *Rattus norvegicus*. A laboratory experiment was conducted using five groups of male rats: three treatment groups receiving burdock root extract at concentrations of 15%, 30%, and 45%, and two control groups—one treated with povidone iodine (positive control) and the other with a basic gel (negative control). Results demonstrated that 30% and 45% burdock root extract significantly improved wound healing compared to both control groups, with the 45% concentration showing the greatest efficacy. These findings suggest that *Arctium lappa L.* extract, particularly at higher concentrations, can enhance the wound healing process and may serve as a viable alternative to conventional treatments.

Keywords: Burdock root extract; extract; rats; wound healing.

INTRODUCTION

Our skin is key to our survival, as the sense of touch, maintains physicochemical and termal homeostasis, acts as a reservoir of essential nutrients, provides passive and active defense, and responds to trauma and injury. The skin also has a role as a body protector from pathogenic agents.[1] Maintaining skin function requires strong and effective mechanisms to protect against trauma, disruption, repair and replacement of critical skin functions when damaged or lost.[2] The incidence of injuries is increasing every year, both acute and chronic wounds. A recent study showed the prevalence of patients with wounds is 3,50 per 1000 population. The majority of injuries in the world's population are wounds due to surgery/trauma (48%), leg ulcers (28%), and decubitus ulcers (21%).[3] Wounds are changes in tissue continuity in cellular and anatomical terms, which can occur in the skin and oral mucosa and continue in the wound healing process.[4] Skin wound healing is the process in which the skin repairs itself after injuries caused by surgery, trauma and burns.[2] Achieving faster healing with fewer side effects is still one of the most important medical goals because it can reduce the risk of infection, complications, and costs.[5] The use of traditional plants for wound healing is based on their ability as antiseptic, antiinflammatory, astringent and antibacterial.[6] The

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use of herbal plants has been accepted by almost all countries in the world. In developed countries, the use of certain herbal plants is very popular. [7] While in developing countries, where standardized health services are limited, herbal plants are usually preferred, as cheap and accessible treatments for disease management. In Indonesia, traditional plants are still widely used in society, both rural and urban. One of the plants that is not yet known but has many benefits is burdock *(Arctium lappa* L.). [8]

Burdock is a plant known as burdock that can be found all over the world which considered a weed.[9] This plant is traditionally used to treat infections such as sore throats, boils, rashes and various skin problems. Many studies have investigated the biological various parts of the burdock, such as anti-microbial, anti-pyretic, anti-inflammatory, anti-hepatotoxicity and antioxidant activity. Compounds found in burdock roots are classified into lignans, flavonoids, and phenolic acids. Two main lignans found in roots are arctigenin and arctiin which have the potential as anti-inflammatory. Arctigenin is a bioactive compound that acts as an anti-inflammatory agent by controlling cytokines and the NF-B signaling pathway. When injured, the body initiates an inflammatory process characterized by an increase in proinflammatory cytokines such as IL-1β, TNF-α, and IL-6. By inhibiting the activation of the NF-B signaling pathway, which is involved in the expression of inflammatory genes, arctigenin helps reduce inflammation caused by injury. [10] Arctiine is also anti-inflammatory, which stimulates and agitates as a powerful antioxidant. Arctiine increases the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) to reduce oxidative stress generated during the inflammatory process. By reducing the damage caused by free radicals, this antioxidant activity helps to accelerate the passage from the inflammatory phase to the proliferative phase. Arctiine also stimulates macrophages to increase phagocytosis, essential for the elimination of microorganisms and cellular debris during the inflammatory phase. [11] Other bioactives including Lignans, quercetin, chlorogenic acid, and inulin have anti-inflammatory and antioxidant properties, modulate immune responses, reduce oxidative stress, and support wound healing and immunity. [12] Flavonoids such as luteolin and quercetin can clean up free radicals and act as anti-inflammatories. Phenolic acids in burdock roots such as caffeoylquinic acid derivatives and chlorogenic acid show strong antioxidant activity. In addition, a fatty acid derivative called oleamide is also found in burdock roots as an anti-allergic agent by inhibiting the release of histamine and producing IL-4 and TNF-α.[13] burdock root is used as a blood purifier, and believed to clear toxins from the bloodstream.[14] Burdock root also contains other chemical compounds such as inulin, essential oils, tannins, resins, sugar, iron, and vitamin C.[5] Tannins function as an astringent which causes shrinkage of the skin pores, hardens the skin, and stops light bleeding.[15] Vitamin C has a role in forming and maintaining collagen during wound healing and can prevent bleeding from the vascular component of connective tissues.[16] Burdock plant studies are more on the stems and leaves. [17] The renewal of this research burdock examines the roots. Research studies roots contain rich protein, oligosaccharides, and other nutrients, and also contain polyphenols, and aldehydes.[18] The content of chemical compounds are tested phytochemically that burdock roots contain saponins, flavonoids, alkaloids, tannins, arctigenin and arctiin function as anti-inflammatory, antioxidants play a role in the wound healing phase.[19,20] This research aims to see the potential of burdock root as an alternative wound healing agent.

MATERIAL AND METHOD

The research was an experimental laboratory conducted at the Pharmacy, Science and Technology Laboratory of Al-Irsyad University, Cilacap from March to June 2023. The protocol of animal research has been approved by The Medical

Research Ethics Committee Fakultas Kedokteran, Universitas Jenderal Soedirman (UNSOED), No. 070/KEPK/PE/V/2023. The materials used were burdock root, 96% ethanol, basic gel, normal saline solution (0.9% NaCl), ketamine, alcohol swabs, povidone iodine. Fresh burdock roots were washed and thinly sliced and then dried in an oven at 50°C for 2x24 hours. The dried simplicia was then crushed to form a powder. As much as 200 g of simplicia powder was put into the maceration container and 300 ml of 96% ethanol was added, stored at room temperature for 3x24 hours with stirring once per day.[21] After soaking for 3 days, the solution was filtered and evaporated using a water bath at 50°C to get the crude extract.

This study obtained burdock root ointment we have prepared it by referring to the dosage of the previous research formulation conducted by Widyawati et al. [22] while the use of gel-based preparations allows for the enhancement of bioavailability, controlled release, and optimal wound environment, ensuring that the bioactive components in the extract work effectively in the healing process. [23]

Table 1. Ointment Formulation

Group Treatment	Burdock Root Extract (g)	Vaseline Album (g)	Ointment (g)
Negative Control (Basic gel) (%)	-	15	15
15	2,25	12,75	15
30	4,5	10,5	15
45	6,75	8,25	15

Before making a wound on the back of the rat, the hair was shaved and disinfected using an alcohol swab. The rat was anesthetized using ketamine at a dose of 50 mg/kg BW intramuscularly, then an incision was made in the back area parallel to the vertebrae using a scalpel to form a 2 cm long wound with a depth of 0,25 cm. Wound care is done shortly after the wound occurs. The wound was cleaned using normal saline (NaCl 0,9%) and then performed according to the treatment group. Treatment is carried out every three days for 14 days until the wound shows signs of healing, such as granulation growth, no swelling (edema) in the wound area, redness around the wound and wound length in cm units. The application was completed twice daily for 14 days, in the morning and the evening. The length of the wound was measured on days 3, 6, 9, 12, and 14 before the ointment was reapplied to track the duration of wound healing using macroscopic observation criteria. On day 14, the rat skin was examined under a microscope. [24]

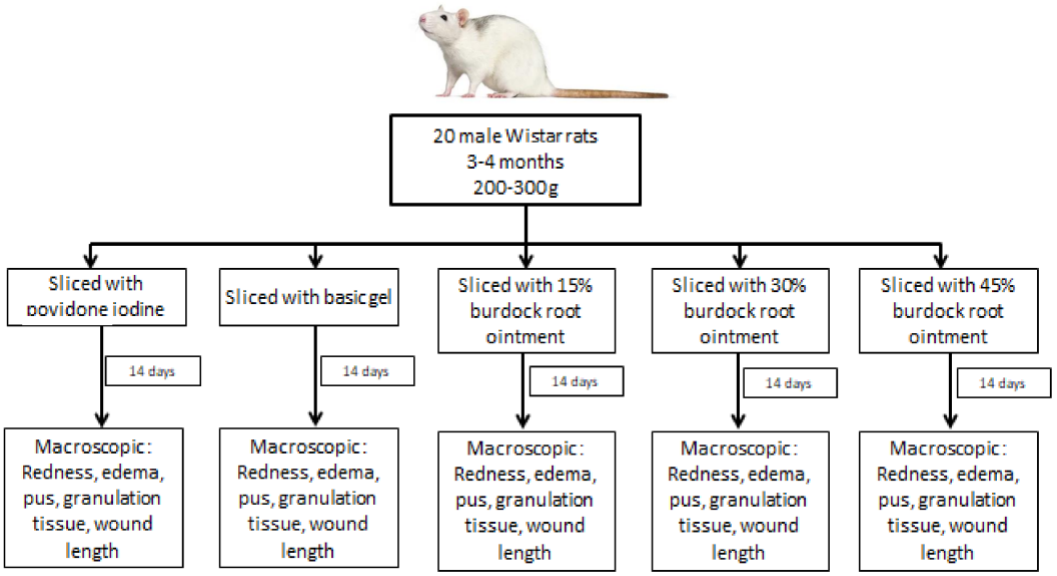

Figure 1. Scheme of animal experiments

Data analysis using the parametric test. The first step was to test the normality using Shapiro-Wilk because the number of samples was less than 50. Then, the data homogeneity test was carried out using the Test of Homogeneity of Variances. After fulfilling the requirements of the parametric test, a One-Way Anova test was carried out to find out whether there was a significant variance in the data significantly different or not. This test was significant if the p-value <0,05. After that, the LSD post hoc test was carried out to see a more meaningful treatment of wound healing in white rats. Data were not normally distributed, an alternative test was performed using the Kruskal-Wallis test and followed by the Mann-Whitney test to determine which treatment had the highest significant value for wound healing in white rats with a significance level of α<0,05. The Kruskal-Wallis Test is a non-parametric alternative to ANOVA that is most appropriate to use because it is the comparison of 4 groups of herbal dose formula groups on wound healing. This test examines whether there is a significant difference between the medians of two or more groups that are not normally distributed. The Mann-Whitney U Test (Wilcoxon Rank-Sum Test): If you only compare two groups (for example, a group with herbal doses and a control), then the Mann-Whitney can be used. This is an alternative to the t-test for data that is not normally distributed. [25]

RESULTS AND DISCUSSION

The results of macroscopic observation of wound healing in male rats can be seen in the table.

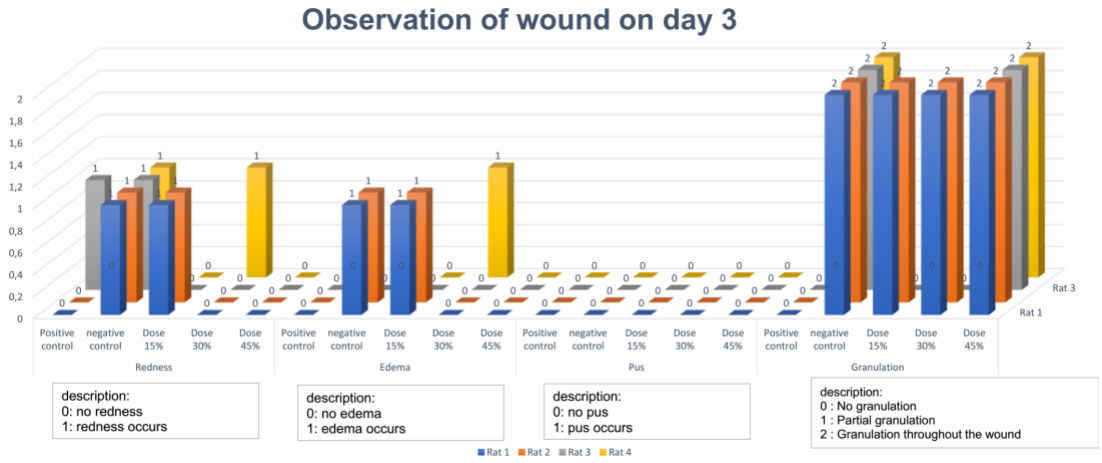

Figure 2. Observation of wound on day 3 includes observation of redness, pus, granulation in the positive control, negative control, dose 15%, dose 30% and dose 45% rat groups.

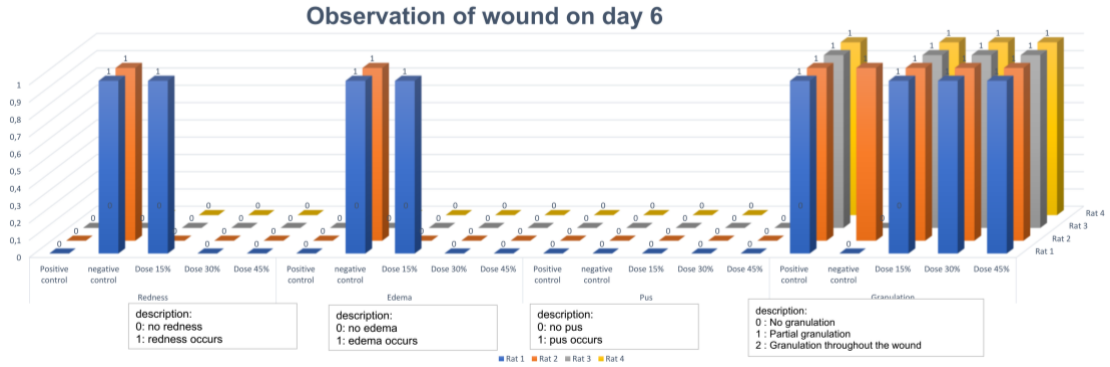

Figure 3. Observation of wound on day 6 includes observation of redness, pus, granulation in the positive control, negative control, dose 15%, dose 30% and dose 45% rat groups.

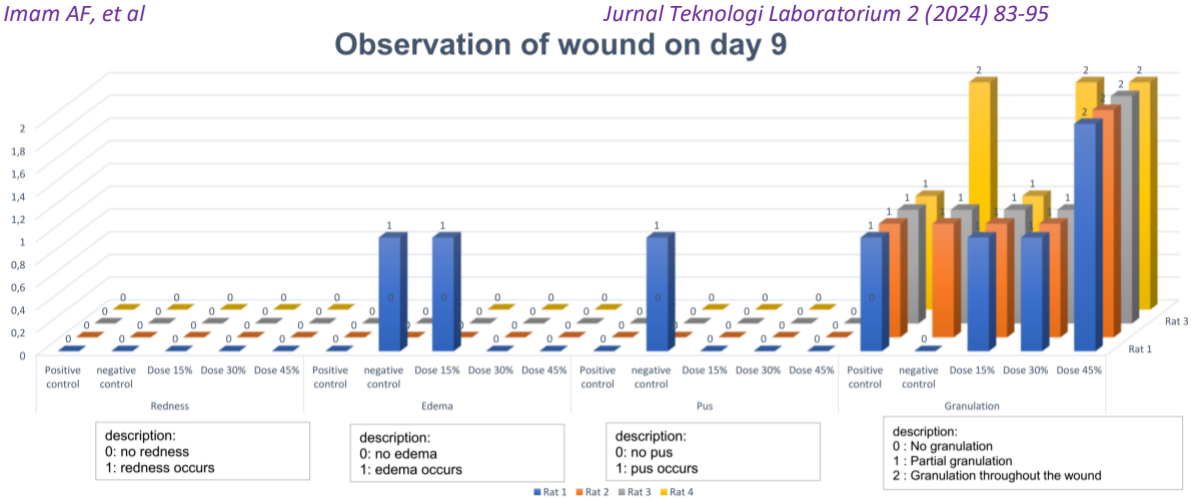

Figure 4. Observation of wound on day 9 includes observation of redness, pus, granulation in the positive control, negative control, dose 15%, dose 30% and dose 45% rat groups.

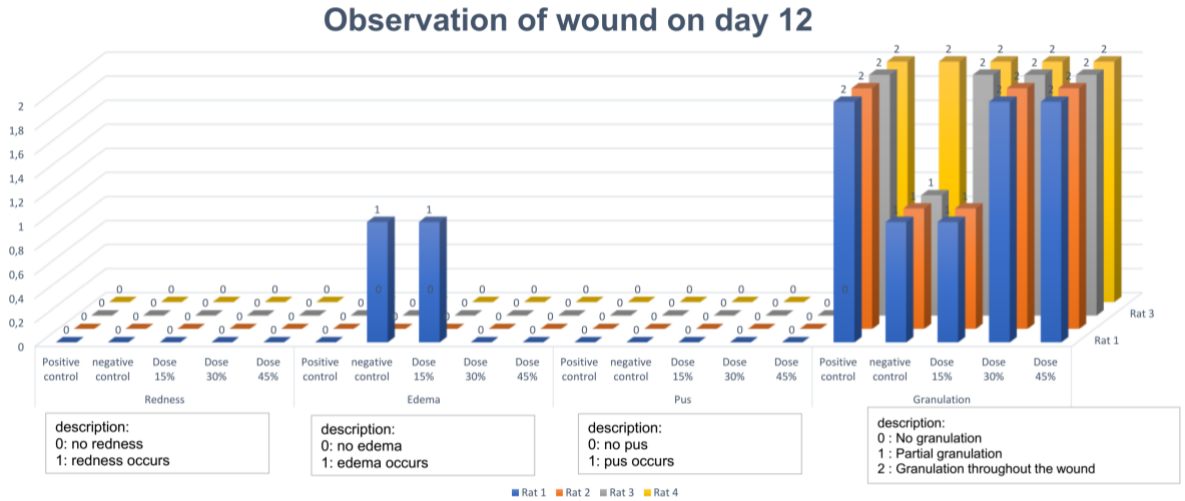

Figure 5. Observation of wound on day 12 includes observation of redness, pus, granulation in the positive control, negative control, dose 15%, dose 30% and dose 45% rat groups.

There are three phases in the wound healing process, namely the inflammatory phase, the proliferation phase, and the remodeling phase, which are mutually sustainable.[6]

1. The healing process in the inflammatory phase

In this section, we will discuss aspects that are observed macroscopically during the wound healing process in the inflammatory phase. Observations made included redness around the wound edema around the wound, and pus fluid in the incision.

a. Redness

Based on the results of the study on day 3, it was found that in the negative control group, redness occurred in all samples. The positive control group and test treatment group 2 (30%) had one sample with redness around the wound. Test 1 (15%) 2 samples had redness around the wound and in the test treatment group 3 (45%) there are four samples without redness around the wound.

When an injury occurs, vasoconstriction occurs in the arteries and capillaries to help stop bleeding. This process is mediated by epinephrine, norepinephrine, and prostaglandins released by injured cells. Blood vessels will enter stage vasodilation after 10 to 15 minutes after injury. Vasodilation of blood vessels is mediated by histamine, serotonin, prostaglandine, and kinins which cause increased blood flow to the injured area and increased capillary permeability.

Increased blood flow to the injured area causes the injured area to appear red and warm.[26]

The acceleration of redness around the wound in the treatment group is thought to be due to the effect of the active compounds derived from burdock root extract as anti-inflammatories and the presence of flavonoid compounds when applied to the skin inhibits bleeding. Flavonoids also function as antibacterials by forming complex compounds extracellular proteins that disrupt the integrity of bacterial cell membranes and tannin compounds are antibacterial by interfering with the permeability of bacterial cells as astringents.[27] Tannins interact with cell surface proteins to form complexes that reduce blood vessel permeability, helping to control fluid exudation during the inflammatory phase. They also have an astringent effect, which accelerates coagulation and helps prevent infection. Tannins are also known to reduce the activation of MMPs (matrix metalloproteinases) enzymes responsible for the degradation of the extracellular matrix during inflammation, thus maintaining tissue integrity during healing. [28] Astringent is a shrinking surface or substance that is protective against the mucosa and can agglomerate protein.[29] Flavonoids can reduce the intensity of redness in wounds by stopping bleeding.[30] Flavonoids act as powerful antioxidants that play a role in inhibiting the NF-κB pathway, which is a major pathway in the inflammatory response. By inhibiting NF-κB activation, flavonoids can reduce the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, which are important during the inflammatory phase. In addition, flavonoids also increase the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which reduce oxidative damage during inflammation and the transition to the proliferative phase. [31] In addition, the role of arctigenin has significant anti-inflammatory activity through inhibition of the JAK/STAT and MAPK pathways. This pathway is important for the production of inflammatory cytokines during the inflammatory phase. Arctigenin also decreases the production of nitric oxide (NO) and prostaglandin E2 (PGE2) through inhibition of the COX-2 and iNOS enzymes, which contribute to reduced inflammation. Arctiin also works by inhibiting NF-κB and MAPK pathways. This reduces the release of inflammatory mediators and helps reduce the infiltration of inflammatory cells such as macrophages and neutrophils into the wound area. Arctiin increases the phagocytic activity of macrophages, which is important in clearing cellular debris during the inflammatory phase and helping the transition to the proliferative phase. [32]

b. Edema

During the inflammatory phase, mast cells release biological substances, namely histamine. Histamine is a vasoactive amino that is released by mast cells after injury and plays an important role in vascular dilatation and permeability, causing plasma to move from the intravascular to the extravascular and cause edema. Vasodilation that occurs in the blood vessels helps inflammatory cells from the vessels to the wound area.[26]

Based on the results of observations of edema on day 3, in the negative control group and test group 1, there were two samples with edema. In the positive control, no edema was found in all samples. In the test group there was one sample with edema. Edema in the test treatment group 1 (15%) and test 2 (30%) have a gradual reduction in the area of edema seen on day 6, the samples that have edema became one, and others are test group 1 (15%) and observations on day 9 to day 14 edema in the control group negative and in the test treatment group 1 (15%) there was one sample each that still had edema.

Swelling in a wound that does not heal can be caused by a germ or bacterial infection that enters the wound which is left open [33] Edema that occurred in the negative control group and others are testing group 1 (15%) was suspected because the wound had an infection which resulted in the wound becoming swollen After all the white rat is a rodent and likes to dig holes, that is what makes the white

rat like to dig into the husks causing the husk dirt to enter the wound which can later cause the wound to become infected. Whereas the absence of edema around the wound in the positive control group and the treatment group, namely test 2 (30%) and test 3 (45%), is suspected to be due to the effect of the essential oil content derived from burdock root extract. Essential oil a function as a wound healing agent that prevents bacterial infection from entering the wound.[5]

Tannins contain anti-bacterial compounds with a mechanism of shrinking the cell wall so that it inhibits the permeability of bacteria to develop.[34] Flavonoids are anti-imflammatory so they can reduce inflammation and help reduce pain, if there is bleeding or swelling of the wound.[35]

c. Presence of pus

Based on the results of the research that has been done, it was found that the presence of pus only occurred on day 9, in the negative control group, was one sample that had pus. While all samples in the control group were positive, and the treatment group test 1 (15%), test 2 (30%), test 3 (45%) did not have pus on the wound.

The absence of pus in the treatment group was thought to be due to the effect of the content of tannins, saponins and essential oils derived from burdock root extract.[36] Saponins have the ability as cleansers and antiseptics which function to kill or prevent the growth of microorganisms and tannins are antibacterial by interfering with the permeability of bacterial cells and as an astringent which can cause closing of skin pores, hardening the skin, stopping exudate and light bleeding.[27]

The use of 10% povidone iodine for wound care in the positive control group also affected reducing the amount of wound fluid exudate in the study sample because povidone iodine was able to kill bacteria, germs, fungi, viruses, protozoa, and spores by working directly to quickly kill germs (bactericidal), not inhibiting the development of germs (bacteriostatic).[26]

2. The wound healing process in the proliferative phase

In the proliferative phase there is a decrease in the number of inflammatory cells, reduced signs of inflammation, the appearance of proliferating fibroblast cells, the formation of new blood vessels, epithelialization and wound contraction. fibroblasts will migrate to the wound area and begin to proliferate until their numbers are more dominant than inflammatory cells.[26] In the proliferation phase, tissue granulation and shortening of the wound length were observed.

a. Granulation tissue

Observations of granulation tissue on day 3 found that in the negative control group there was no granulation tissue. In the positive control group and the test treatment group 3 all samples had partial granulation. Test groups 1 and 2 contained three partially granulated samples. These results prove that the growth of granulation tissue in the three treatment groups that were given burdock root extract was faster than the negative control group that was given basic gel. The growth of wound granulation tissue in the treatment group is thought to be due to the effects of saponins, flavonoids, and tannins derived from burdock extract. Saponin compounds are steroids or triterpenoid glycosides that can stimulate vascular endothelial growth factor (VEGF) and increase the number of macrophages migrating to the wound area thereby increasing fibroblasts in the wound tissue.[26] Saponins also can stimulate the formation of collagen.[27] Tannins help the wound healing process by increasing the number of capillary blood vessels and fibroblast cells.[5] Flavonoids can help wound healing by increasing collagen formation, reducing macrophages and increasing the number of fibroblasts.[26] Tannins accelerate collagen synthesis by stimulating TGF-β and stimulating fibroblast activity. Tannins also induce angiogenesis by increasing VEGF expression, which is necessary for tissue healing. In addition, the antioxidant

properties of tannins protect fibroblast cells from oxidative stress, allowing the healing process to occur more quickly and efficiently. [28]

Based on the results of statistical tests, all treatment groups had a significant effect on the accelerated growth of granulation tissue in the wounds of white rats, but what was more influential was burdock root extract concentration of 45%, then 30% and 15% this was also seen from the results of macroscopic observations where on day 12 the treatment group test 2 (30%) and test 3 (45%) all samples have granulation in all wounds the same as compared to the positive control but not to the test treatment group 1 (15%)). The treatment group test 1 (15%) experienced slow granulation growth as seen from the statistical test test 1 (15%) which was not significantly different from the negative control group. This was presumably because the 15% concentration contained a small amount of burdock root so ingredients such as saponins, flavonoids, and tannins derived from burdock extract were less effective in forming granulation tissue in test group 1 (15%). Flavonoids enhance fibroblast proliferation by increasing the expression of growth factors such as TGF-β and VEGF, which stimulate angiogenesis (formation of new blood vessels) and collagen synthesis by fibroblasts. Flavonoids' antioxidant activity also protects fibroblasts from oxidative stress, thereby enhancing their regenerative capacity during the proliferative phase. Arctigenin stimulates fibroblast proliferation and increases collagen synthesis through activation of the TGF-β/Smad pathway, which is important in the process of extracellular matrix formation. [37] Arctigenin is also known to stimulate angiogenesis by increasing the expression of VEGF and FGF (fibroblast growth factor), which increases blood supply to the wound area and accelerates healing. Arctigenin facilitates fibroblast proliferation and increases collagen deposition by stimulating the expression of COL1A1 and COL3A1, genes that encode the synthesis of type I and type III collagen. Arctigenin is also known to reduce the activity of MMPs, which prevents the degradation of collagen and extracellular matrix, thereby accelerating the recovery of tissue structure in the proliferative phase. [32]

b. Wound Length

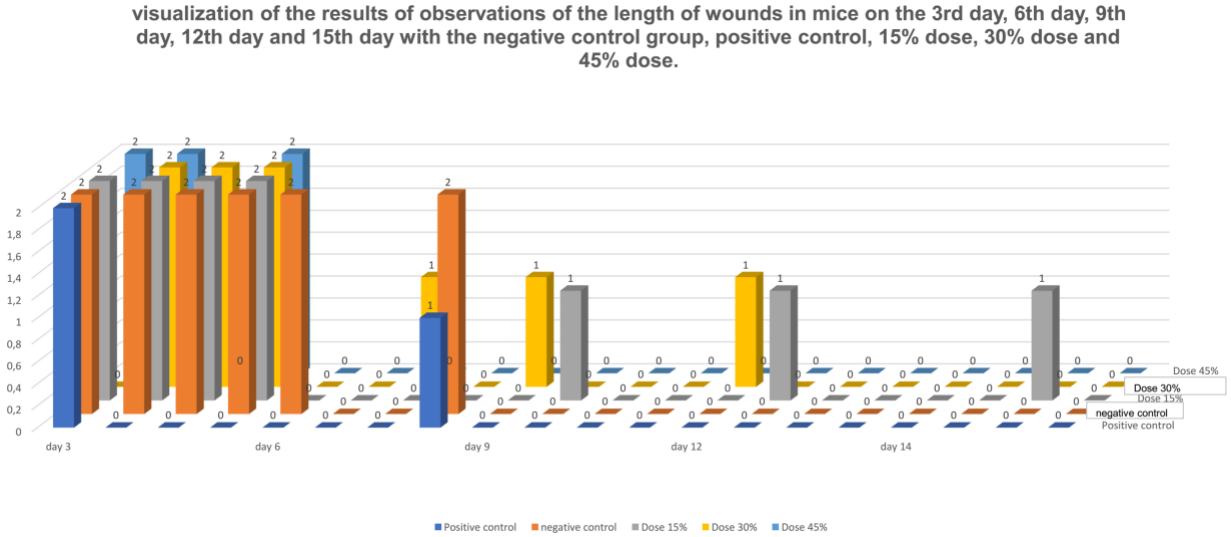

Figure 6. visualization of the results of observations of the length of wounds in mice on the 3rd day, 6th day, 9th day, 12th day and 15th day with the negative control group, positive control, 15% dose, 30% dose and 45% dose.

After granulation tissue is formed, epithelialization or growth of epithelial tissue will begin to occur. Epithelial cells that grow will move from the outside of the injured tissue to the inside of the tissue [38] The construction of wound tissue is the last stage of the reconstruction phase of wound healing. Construction will occur 6-12 days after the wound occurs and the wound will close.[39]

In this study the researchers observed the length of the wound starting on the 3rd day after making an incision with a length of 2 cm. The negative control

group ranged from 1.8 to 2 cm. Test group 1 ranged from 1.5 to 1.8 cm. Test group 2 ranged from 1 to 1.5 cm. Test group 3 ranged from 0.9 to 1.3 cm. Then there was a new significant difference that occurred on the 9th day which resulted in the positive group with wound lengths ranging from 0.6 to 0.8 cm. The negative control ranged from 1.4 to 1.5 cm. Test group 1 1 to 1.4 cm. Test 2 ranged from 0.6 to 1 cm. Test 3 ranged from 0.6 to 0.8 cm.

Saponins is a compound that act as antiseptic, stimulate the proliferation of epidermal cells and affect the rate of migration of keratinocytes to the wound area, thereby increasing wound epithelisation. Saponins can alson stimulate the production of type I collagen which plays a role in increasing epithelialization of sittues and wounf closure by inhibiting excessive tissue production.[40]

Based on the results of statistical tests, the treatment group using burdock root extract at a concentration of 15 % had no effect on the accelerated shortening of wound length in white rats. While the treatment group used burdock root extract with a concentration of 45% and 30% had a significant effect on accelerating the shortening of wound length in white rats, but the more influential was the 45% burdock root extract. Samples with a wound length of 0 cm (healed). Burdock root is effective in healing cuts in herbal medicine due to its anti-inflammatory, antioxidant, and fibroblast proliferation activities. In comparison, aloe vera accelerates epithelialization and angiogenesis through polysaccharides and glycoproteins and has strong anti-inflammatory effects.[41] Curcumin *(Curcuma longa)* in turmeric inhibits pro-inflammatory cytokines, increases collagen synthesis, and has antibacterial effects. Gotu Kola *(Centella asiatica)* supports wound healing by stimulating collagen synthesis, fibroblast proliferation, and tissue capillarization.[41] Comparison of burdock root to other herbs and povidone iodine shows that Burdock root contains arctigenin and arctiin which have been shown to have adequate anti-inflammatory and antioxidant properties to accelerate wound healing, especially through reducing inflammation and increasing collagen synthesis.[42] While Aloe vera has a rapid soothing effect and accelerates epithelialization, but does not have strong antioxidant potential like burdock root. Curcumin is superior in terms of inhibiting pro-inflammatory cytokines compared to burdock root, but burdock root is superior in terms of improving tissue remodeling. Comparison Povidone iodine is a conventional treatment that is widely used in wound healing, but its use is more intended to reduce the risk of infection, not to accelerate tissue regeneration like herbs.[43]

Table 7. Kruskal-wallis test of wound length in male rats during 14 days.

Group Treatment	Average wound length (cm)				
	Day 3	Day 6	Day 9	Day 12	Day 14
Basic gel (negative control)	2	1,90	1,50	1,12	0,72
Povidone iodine (positive control)	1,82	0,95	0,70	0,40	0
15%	1,65	1,65	1,20	0,77	0,50
30%	1,30	1,30	0,80	0,55	0,12
45%	1,95	1,15	0,70	0,45	0,05
**P-value*	0,074	0,004	0,004	0,003	0,003

*Kruskal-wallis test

Based on the results of the Kruskal-wallis test above, it was found that the test dose and the positive control did not have a significant effect on the wound on day 3 (p-value>0,005). But it works on days 6 to 15 marked by narrowing of the incision area (p<0,005). [44]

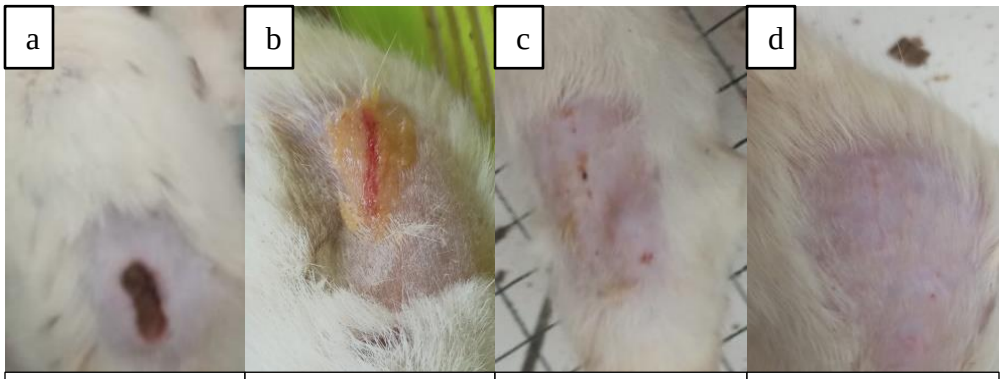

Figure 7. Edema and pus (a), redness (b) granulation (c), wound healed

Many studies examining the effectiveness of Burdock root in wound healing often involve small sample sizes, which can reduce the statistical power of the results. Studies with larger sample sizes are needed to ensure the reliability of the findings. Studies are often limited by short observation periods, usually only a few days to a few weeks. Wound healing is a process that requires long-term observation to assess full efficacy, especially during the tissue remodeling phase. Measurement of wound healing outcomes often relies on visual observation, which can be biased and subjective. The use of more objective techniques, such as histology or molecular measurements of growth factors or proteins, is needed to provide more precise data. Further studies are needed to test the effectiveness of Burdock root extract on different types of wounds, such as burns, diabetic wounds, or pressure ulcers. Combining Burdock root formulations with other treatments, such as co-application of silver nanoparticles or biomaterial scaffolds, may provide a synergistic effect that accelerates wound healing. This combination could also be tested on a larger scale to support the synergistic effect of the two methods.

CONCLUSION

Administration of burdock root extract concentrations of 30 % and 45 % were effective in the wound healing process, both in the inflammatory phase and in the proliferative phase. Based on statistical tests and macroscopic observations there were differences in the effect of burdock root extract concentrations of 15%, 30% and 45% in the wound healing process. Burdock root extract with a concentration of 45 % is most effective in the healing process of cuts in rats.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author upon reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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