ORIGINAL ARTICLE

Increasing The Number of Fibroblast in Incision Wounds in Male Mice (*Mus musculus*) by Giving Aloin Cream: Sharp Incision Method

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ABSTRACT

Introduction: The Elderly lead to decreased fat and water content in the stratum corneum, causing skin to become dry, thin, and easily injured by sharp objects. This study aims to evaluate the effectiveness of aloin cream on the number of fibroblasts in elderly male mice (*Mus musculus*). **Methods:** This research employed a simple randomized sampling, post-test control group design. The sample consisted of 48 male Mus musculus strain mice aged 8 months. There are 4 groups, with each group containing 12 mice. Sacrification was carried out on the 7th and 14th days. Data were analyzed using general linear models, Bonferroni tests, and paired sample t-tests. **Results:** On day 7, the mean number of fibroblasts was 8.11 (K-), 8.77 (K+), 6.33 (P1), and 6.33 (P2). By day 14, fibroblast counts were 5.28 (control -), 6.27 (control +), 6.44 (P1), and 9 (P2). There was an increase in fibroblast cell counts on day 14 in treatment groups 1 and 2. There was a significant increase in fibroblast cell counts in group P2. **Conclusion:** Aloin cream effectively increases the number of fibroblast cells, so it can improve wound healing in male mice (Mus musculus) ($p < 0.05$).
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INTRODUCTION

The composition of the world's population has undergone a change characterized by an increase in the number of people over 60 years old or elderly. By 2050, according to WHO, the number of elderly people worldwide will reach two billion. Data from the Central Statistics Agency (BPS) states that in 2024, the number of elderly people was 12% of the total population of Indonesia. The increase in the number of elderly people has an impact on the health sector, namely the emergence of an increase in degenerative diseases and cancer due to the decline in the function of the organs of the elderly. Generative diseases also target the skin organs of the elderly. The skin of the elderly is aging and presents problems, especially wound healing problems(1–3).

Clinical symptoms of skin aging are characterized by saggy skin, hyperpigmentation and/or hypopigmentation, wrinkles, decreased skin heat and moisture, and slowed wound healing. Histologically, aging is characterized by a dense stratum corneum, which results in slowing of skin turnover, uneven distribution of melanocytes, and even melanocytes. In the basal layer of the epidermis, there is a narrowing of the dermal-epidermal junction. In the dermis, collagen degradation was found with a decreased amount of new collagen regeneration. Fibroblasts senesce, and there is an increase in the amount of elastin. The number of nerve fibers and blood capillaries also decreases(4–6).

A cut occurs when a sharp object scrapes or cuts the skin to a depth of 0.3 cm and a length of up to 1.5 cm. If not treated properly, cuts can become infectious and are characterized by open, painful, and longer-than-deep wounds(7,8). Wounds in the elderly often last for a long time, even more than 8 weeks, and ulcers occur, and do not heal completely. The elderly are more likely to have chronic wounds. Approximately 1.1%-26% of elderly outpatients experience wound ulcers due to a slowdown in wound healing reactions. The elderly experience a decrease in and dysfunction of fibroblast cells, which causes a slow process of wound proliferation

and remodeling. In the inflammatory process, there is increased activation of neutrophils and macrophages, and increased pro-inflammatory cytokines, which results in prolongation of the inflammatory phase and delayed fibroblast proliferation. The result of re-epithelialization may not occur, resulting in a chronic wound (7,9).

Aloin is a phenolic brownish-yellow solid compound with a glycoside group along the hydroxylbenzene carbon chain found in Aloe vera, especially Aloe vera barbadensis Miller. Aloin is a glycosylated anthraquinone consisting of aloin A (barbaloin) and aloin B. Aloin has laxative, anti-microbial, and anti-oxidant effects. This antioxidant effect of aloin can be utilized in the process of accelerating wound healing. Aloin increases skin moisture retention, increases fibroblast production, and migration activity so that the prolongation of the inflammatory phase can be stopped and the wound healing process immediately enters the proliferation and remodeling stages (10–12).

Research on the effect of aloin on accelerating wound healing is still limited. Dewi et al.'s research stated that the administration of aloin extract accelerated the wound healing reaction by increasing the number of fibroblast cells on the 7th day post-wounding. This study uses direct administration of liquid extracts rather than in the form of creams or gels(10). Li et al's research on the three-layer nanomembrane of Aloin / PVP / PLA states that aloin with nanomembrane technology in vitro can increase the production and migration of fibroblasts, so that it can be used as a breakthrough to accelerate wound healing (12).

Research on the use of aloin cream on incision wound healing in elderly skin has never been done. Based on existing research, aloin can be a breakthrough in accelerating wound healing, so researchers want to investigate giving aloin to elderly mice modeling treated with incision wounds. Mice will be given two doses of aloin cream, namely 1.25 mg and 2.5 mg in cream form, and the number of fibroblast expressions will be counted on the seventh day and the fourteenth day.

The World Health Organization (WHO) defines older adults as 60 and above. According to United Nations data on World Population Ageing, there were 705 million older adults in 2019, 9.18% of the global population, expected to rise to 2 billion by 2050. In Indonesia, the Central Statistics Agency (BPS) reported that 10.48% of the population would be elderly in 2022, down from 10.82% the previous year. As people age, they experience diminished organ function and decreased fibroblast tissue in the skin, leading to various health issues, particularly skin problems in the elderly (1–4). Cuts occur when a sharp object scratches or cuts the skin to a depth of up to 0.3 cm and a length of up to 1.5 cm. If not adequately managed, cut wounds can become infectious and are characterized by being open, painful, and more prolonged than deep(3,5).

In older adults, the epidermal layer thins, reducing the contact area between the dermis and epidermis, which decreases nutrient exchange. Consequently, even mild trauma can cause the skin to rupture. Additionally, the proliferative ability of basal cells and the number of mast cells and fibroblasts in the dermis are lower in older adults than in younger individuals, impacting collagen and elastic fibers (6,7).

Aloin cream can help enhance fibroblast activity. Aloin is a phenolic compound with a glycoside group along a hydroxylbenzene carbon chain, with a molecular weight of 418.39 g/mol and a chemical formula of C21H22O9. It is an anthraquinone derivative with a glucose molecule attached to the primary benzene ring; if the ring in the CH2OH benzene ring is severed, aloe-emodin is formed, ranging in color from brown to black depending on the concentration(8–10). Aloin enhances the skin's moisture retention, crucial for maintaining suppleness and reducing wrinkles. Skin loses moisture and elasticity as we age, leading to fine lines and wrinkles; aloin can help counteract this by increasing hydration. The A and B compounds in aloe vera bind moisture to the skin, improving hydration and minimizing wrinkles. Fibroblasts, which produce the extracellular matrix, are essential for wound healing and skin restoration. However, fibroblast activity declines with age, resulting in slower healing and older-looking skin. Aloin promotes fibroblast production, aiding faster wound healing in older adults(11,12).

This study involved male mice (Mus musculus) that were monitored closely in the lab. Mice are widely used in medical, genetic, and obesity research due to their ease of breeding and suitability for quantitative studies, making them excellent animal models for examining traits(13). The focus on older mice was chosen because aging processes make wound healing slower in older people. The researchers aimed to determine if aloin gel could increase fibroblast counts in elderly mice. Thus, the study will investigate whether there is an increase in the number of fibroblast cells by comparing the number of fibroblast cells on day 7 and day 14 in the number of fibroblasts in wounds of male mice (Mus musculus) elderly models with aloin cream.

MATERIALS AND METHODS

Experimental Animals

This study is an experimental Post-Test Control Group Design, using four groups: negative control, positive control, treatment 1, and treatment 2. The negative control group is mice with topical administration of NaCl 0.9% as wound medication. The positive control group is mice with topical povidone-iodine as wound medication. Treatment group 1 is mice with 1.25 mg aloin cream as wound medication. Treatment group 2 is mice with 2.5 mg of aloin as wound medication. According to the Federer formula, the number of mice per treatment group is 6. In this study, each group will use 12 mice because mice skin samples will be taken on the seventh and fourteenth days. The mice used are male Mus musculus mice aged 28 weeks, healthy and active during the elderly modeling process. Mice will be acclimatized for 7 days. On the 8th day, the mice will enter into elderly modeling. Mice are given high-fat and high-protein feed. The mice are given exposure to ultraviolet C light with a wavelength of 185 nm for 9 days with a duration of 15 minutes on days 8 to 11, a duration of 20 minutes on days 12 to 14, and 25 minutes on days 15 to 18. On day 19, healthy and active mice are declared as mice that meet the inclusion requirements to participate in the study.

Aloin Cream

Aloe vera barbadensis Miler is sourced from Kalimantan and processed at the MarkHerb laboratory. The extraction of aloin from aloe vera achieved a yield of 99.49%, with Aloin A making up 57.88% and Aloin B 42.12%; other chemicals comprised 0.51%. The aloin is sent to PT Micca Industrial for cream manufacturing, with this study's cream containing 1.25 mg and 2.5 mg of aloin.

Wounds in Elderly and Adult Mice

On the first day, all mice from the four groups will be treated with wounding. The first step is to shave the mice on the back area of 3 x 3 cm and administer topical lidocaine as an anesthetic. The wound is done with a skin incision of 20 x 10 mm, ±1-2 mm deep. Pinch the skin with tweezers and use surgical scissors to excise the marked area. After the wounding, the mice were given wound medication according to the group of mice. The wound was covered with gauze after wound dressing. The medication was given once a day in the morning for 14 days. On the seventh day, 6 mice per group were euthanized for skin tissue collection. On the fourteenth day, 6 more mice were euthanized for skin tissue collection.

Histopathology Preparations

The skin around the incision is cleaned with physiological NaCl and cut in half. One part is soaked in 7.4% Phosphate Buffer Saline (PBS) and stored at 4℃, while the other is soaked in a 4% paraformaldehyde (PFA) solution and stored at room temperature. Automatic Tissue Processing is used to create slides. Histopathology skin samples undergo fixation, dehydration, infiltration, clearing, paraffin infiltration, embedding, and sectioning. Histological preparations are observed under a binocular microscope, with fibroblast cell counts performed at 400x magnification across three fields. Fibroblast counts are calculated symmetrically from the left corner to the right until all fields are assessed, and the average number of fibroblast cells per sample is computed (13). Fibroblast cells are large, flat, branched cells with a fusiform shape. In connective tissue, the fibroblast nucleus appears pale when stretched, while in the presentation of 33 slices, fibroblasts appear shrunk and dark with basic staining (14). The Faculty of Medicine Ethics Committee of Universitas Baiturrahmah approved the experimental protocols, as indicated by certificate number 155/ETIK-FKUNBRAH/03/10/2023

Data Collection and Analysis

The data taken is the number of fibroblast cells found in histological preparations of mice skin. Data for each group will be seen as the mean value and standard deviation in univariate analysis. Then each group was tested for normality with Shapiro-Wilk. The normality test showed normal data distribution. Furthermore, the General Linear Model test was carried out with Bonferroni's post-hoc as a bivariate test of the data. Data is declared significant if the p-value is <0.05. The degree of confidence in this study is 95%.

This study explores Geriatrics, Pharmacology, Anatomical Pathology, and Histology. The aim is to conduct laboratory experiments using a Post-Test Control Group Design, measuring or observing outcomes after treatment. Preliminary research was performed to create elderly model mice. The study occurred from March 2023 to January 2024 at the Biomedical Laboratory and Anatomical Pathology, Faculty of Medicine, Baiturrahmah University. The samples consisted of 28-week-old adult male mice (Mus musculus) meeting the inclusion criteria of being healthy and active during the elderly modeling process without experiencing pain. Exclusion criteria included mice that died during the study, developed infected wounds, or were inactive. The mice were acclimated to a standard room temperature (25 ± 2°C), humidity, and regulated lighting (12 h light and dark) and were provided with regular rodent food and free access to water (13). After one week of acclimatization, the mice were randomly divided into four groups of twelve: negative control (C-) elderly mice with 0.9% NaCl, positive control (C+) elderly mice with povidone-iodine, treatment group (P1) with 1.25 mg aloin cream, and treatment group (P2) with 2.5 mg aloin cream. Six mice from each group were sacrificed on days seven and fourteen. The research flow carried out is as shown in Figure 1.

RESULTS

Table I presents the number of fibroblast cells in elderly male mice skin histology on days 7 and 14. On day 7, the highest mean number of fibroblast cells was observed in the positive control group (C+), with a mean of 8.77 ± 2.97, followed by the negative control group (C–) with 8.11 ± 2.69, treatment group 2 (T2) with 7.33 ± 1.05, and treatment group 1 (T1) with 6.33 ± 2.05. On day 14, the highest mean number of fibroblast cells was observed in treatment group 2 (T2), which received 2.5 mg aloin cream, with a mean of 9.66 ± 3.15. In contrast,

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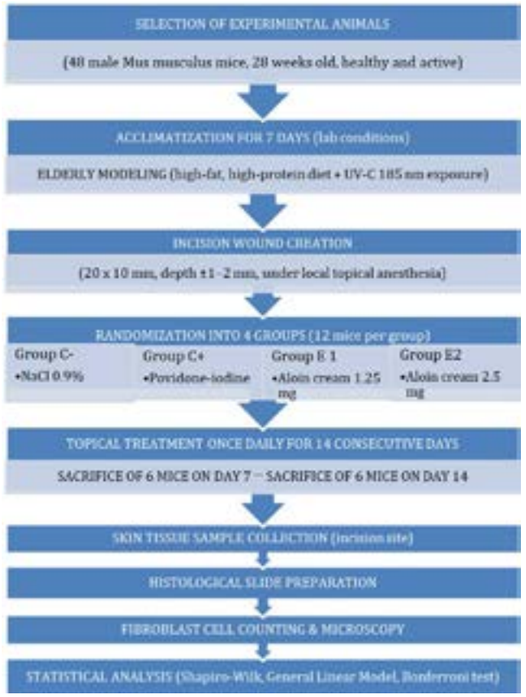

Figure 1: Research Flowchart

Table I. The Number of fibroblast cells in the skin elderly male mice histology

Groups	N	Mean± Std. Dev On 7th Day	Mean± Std. Dev On 14th day	Significant test
C-	6	8.11±2.69	5.28±1.34	0.016
C+	6	8.77±2.97	6.27±1.32	
T1	6	6.33±2.05	6.44±1.20	
T2	6	7.33±1.05	9.66±3.15	

Notes
C -: Negative control group
C +: Positive control group
T1: Treatment control group
T2: Treatment control group

the negative control group showed a decrease from 8.11 ± 2.69 on day 7 to 5.28 ± 1.34 on day 14. These findings indicate that treatment with aloin cream, particularly at a dose of 2.5 mg, helped maintain and increase fibroblast cell numbers during the wound healing process.

As shown in Table II, the Shapiro-Wilk normality test showed that the data were normally distributed, with p-values greater than 0.05. The homogeneity test also showed homogeneous variance, with p-values greater than 0.05. Therefore, the data met the assumptions for parametric analysis. The General Linear Model test showed a significant difference among the groups, with a p-value of 0.016, indicating that aloin cream administration had a significant effect on fibroblast cell counts in elderly male mice with incision wounds.

Table II. Assumption tests and overall statistical analysis of fibroblast counts

Analysis	Test used	Result	Interpretation
Normality	Shapiro-Wilk test	p > 0.05	Normally distributed data
Homogeneity	Homogeneity test	p > 0.05	Homogeneous variance
Overall comparison	General Linear Model	p = 0.016	Significant difference among groups

Notes: A p-value of <0.05 was considered statistically significant.
The overall p-value was taken from the General Linear Model analysis reported in the results section.

Table III presents the pairwise comparison of fibroblast counts. The Bonferroni post-hoc test showed a significant difference between the negative control group (C–) and treatment group 2 (T2) on day 14, with a p-value of 0.027. This indicates that 2.5 mg aloin cream produced a significant increase in fibroblast cell counts compared with the negative control group after 14 days of treatment. Within-group comparison using the paired sample test also showed significant differences between day 7 and day 14 in the negative control group and positive control group, with p-values less than 0.05. However, no significant differences were observed between day 7 and day 14 in treatment group 1 and treatment group 2, with p-values greater than 0.05.

DISCUSSION

When a wound occurs in the skin, tissue repair begins with the body's homeostasis reaction, activating extrinsic and intrinsic pathways to prevent blood loss. The healing process begins with the inflammatory stage shortly after a wound occurs. The body responds by activating cytokines, molecular mediators, and macrophages. The cellular immune system will sterilize the wound and prevent an infectious reaction. Platelets release chemokines, necrotic cell debris is absorbed, and pathogenic material is neutralized from the wound site (15,16).

The next stage is fibroblast cell migration, which occurs on the fifth to seventh day of wound healing, signaling that the proliferation process is about to begin. Fibroblast cells are responsible for synthesizing and repairing the extracellular matrix (ECM) as the skin's structural framework. Fibroblast cells that migrate to the wound site will undergo differentiation into myofibroblasts under the influence of the cytokine transforming growth factor β (TGF-β). Myofibroblasts will form wound contractures after injury(15,17,18). Fibroblast cells are derived from fibrocytes, mesenchymal progenitor cells in the bone marrow. The process of fibroblast migration to the wound site is activated by pro-inflammatory cytokines such as interleukin (IL)-4, IL-13, and interferon (IFN)-ɣ. With aging skin, fibroblast migration slows down and ECM formation is disrupted, resulting in delayed re-epithelialization and even chronic wounds. The condition of dermal collagen in aging skin is also unfavorable, with collagen and matrix destruction worsening the wound-healing process (10,19). Another

Table III. Pairwise comparison of fibroblast counts

Comparison	Time point / comparison period	Test used	p-value	Interpretation
C– vs T2	Day 14	Bonferroni post-hoc test	0.027	Significant
C–: day 7 vs day 14	Within-group comparison	Paired sample test	<0.05	Significant
C+: day 7 vs day 14	Within-group comparison	Paired sample test	<0.05	Significant
T1: day 7 vs day 14	Within-group comparison	Paired sample test	>0.05	Not significant
T2: day 7 vs day 14	Within-group comparison	Paired sample test	>0.05	Not significant

Notes: C–: negative control group; C+: positive control group; T1: treatment group treated with 1.25 mg aloin cream; T2: treatment group treated with 2.5 mg aloin cream.
Only p-values available from the supplied results text were included. Replace <0.05 or >0.05 with exact p-values if available.

detrimental condition to elderly wound healing is the presence of senescent cells in the skin. Protracted inflammatory processes are influenced by inflammatory conditions, namely pro-inflammatory cytokines IL-6 and IL-8, which provide a low-grade inflammatory response. Fibroblast cells in the elderly can also be senescent fibroblast cells, so they do not provide a complete wound-healing effect even though fibroblast cell migration has occurred. The result is a decrease in fibroblast differentiation, resulting in inhibition of ECM formation (19,20).

In this study, fibroblast cell migration was found on the seventh day, with the highest number of fibroblasts found in the control group. The negative control group received 0.9% NaCl, and the positive control group was given povidone-iodine. 0.9% NaCl is used as a wound medication because NaCl has the effect of keeping the skin moist, keeping the granulation tissue from drying out, so that the inflammatory and proliferation processes run well. Povidone-iodine, an antiseptic made from iodine and polyvinyl pyrrolidone, is used to clean wounds, prevent infection, and accelerate healing by inhibiting microbial growth (8,9). In the treatment group that received aloin, the number of fibroblasts expressed was less than the control group but increased until day 14. In treatment 2 with 2.5 mg aloin cream, the number of fibroblasts was more than in treatment group 1(21,22). Previous research by Li et al. stated that invitro research accelerated wound healing by giving aloin accelerated the process of fibroblast cell proliferation and re-epithelialization. Furthermore, invivo research on aloin administration to incised wounds showed that aloin accelerated the re-epithelialization process, and in histological preparations, it was seen that the collagen produced in the wound tissue treated with aloin was more compact and regular than the control group. Another advantage of aloin is that it prevents scar formation. In this study, the day of highest fibroblast expression in wound healing was not determined (23). Fibroblasts, resembling spindle cells, connect tissue cells, and migrate to the wound site within 3 to 5 days after injury, having a significant impact on granulation and wound closure (10,24). The invitro study by Liu et al. may explain the increase in fibroblasts by aloin. This study used elevated temperatures on cultured cells to produce many free radicals, similar to the skin conditions of the elderly. The administration of aloin in this experiment did not show a significant increase from the third to the fifth dayof the study. However, there was a significant decrease in lipid peroxidation as a free radical. Aloin accelerates the wound-healing process by reducing oxidative stress that is commonly found in old skin and increasing the expression of glutathione, which is an endogenous antioxidant. This reaction will inhibit senescent cells, both senescent immune cells and senescent fibroblast cells present in the wound healing process. Aloin produces migrating fibroblast cells that can proliferate perfectly so that the ECM produced is compact and regular (25). Fibroblasts in ageing skin are senescent, which decreases their ability to produce a compact and organized ECM. Research shows that older skin heals more slowly and scarring may occur. This is what Aloin corrects, by neutralizing the free radicals present in aged skin and activating the migration of fibroblasts that are better able to proliferate and re-epithelialize (11,26,27).

Previous studies support the fact of fibroblast expression on day 14. The administration of aloin with a significantly higher dose gave the highest fibroblast expression compared to the control group. The control group is thought to have entered the remodelling phase on day 14 which is marked by a decrease in fibroblast expression. Although the control group had entered the remodelling phase, there was a possibility that the wound-healing process was not optimal. In aged skin without intervention, fibroblast cells that proliferate are senescent fibroblast cells which can result in wounds not healing optimally, because the formation of ECM is not compact and regular. Other possibilities include wound scabbing (19,20). This study did not include macroscopic wound studies, namely wound area, wound shape, and scab formation. Wound macroscopic research can be used as a suggestion for further research.

CONCLUSION

The administration of aloin cream effectively accelerates wound healing by increasing fibroblast expression in male mice Mus musculus elderly models given a cut wound, with the optimal dose of 2.5 mg of aloin cream. Aloin cream 2.5 mg can be considered an alternative topical therapy to accelerate wound healing in elderly patients, especially those with impaired tissue regeneration due to the ageing process. Clinical studies in elderly humans are needed to confirm the safety and effectiveness of aloin in real clinical conditions. The study's findings have significant practical ramifications,

particularly for advancing natural compound-based wound therapies like aloin. Aloin can shorten recovery times, and improving the quality of life for older patients by speeding up wound healing.

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