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EFFECT OF ALOIN EXTRACT ON THE INCREASE OF FIBROBLAS CELL EXPRESSION ON HEALING OF WOUND WOUNDS OF HORSE WHITE RATS (Rattus norvegicus) BY THE AGING PROCESS

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Abstract

Motivation/Background: The wound healing of aging skin can be assisted by using aloin that increases fibroblast cells. The aim of this research is to determine the effect of aloin extract on increasing fibroblast cells in wound healing in male rats (Rattus norvegicus) with aging process The method research is a post-test control group design. The research sample use twenty-four of six months male rats (Rattus norvergicus) which were divided into 4 groups. Fibroblast assessment was carried out on days 7 and 14 of aloin treatment. Fibroblast data was processed using normality test and significance tests, carried out using the measured repeated test followed by Bonferonni test. The results is highest number of fibroblasts on day 7 was in the control group (+) treated with 10% povidone iodine. The highest number of fibroblasts on day 14 was in treatment group 2 which was given aloin. The statistical test Measure Repeated test said that there was no significant difference between the control and treatment groups p = 0.503 (p> 0.05). However, in the Bonferonni post hoc test, the value of p = 0.000 was obtained, which means that giving aloin can increase the number of fibroblast cells. The conclusions is aloin extract increased the number of fibroblast cells in wound healing of male rats (Rattus norvegicus) with aging process, which has the same effectiveness as povidone iodine.

Keywords: Aloin, Fibroblast, Wound Healing, Aging Process

1. Introduction

Skin deteroriation is a process of gradual degeneration of skin function and capacity. Factors that contribute to skin aging include extrinsic and instrinsic factors. Extrinsic factors include ultraviolet and infrared radiation and air pollution. Intrinsic factors consist of genetics, cellular metabolism and hormones. Instrinsic aging occurs with atrophy of the epidermal layer so that the skin is easily injured after minor trauma, decreased basal cell proliferation ability, in the dermis layer there is a decrease in the number of fibroblast cells, collagen fibers, elastin fibers and mast cells (1-4). Fibroblast proliferation determines the final outcome of wound healing. Fibroblasts produce collagen that will anchor the wound and influence the re-epithelialization process that will close the wound. Inhibited fibroblast growth can result in decreased wound healing potential (5,6)

Skin deterioration is the process of gradual degeneration of skin function and capacity. Factors that contribute to skin aging include extrinsic and instrinsic factors. Extrinsic factors, such as ultraviolet and infrared radiation and exposure to air pollution, can accelerate the skin aging process. On the other hand, instrinsic factors, which include genetics, cellular metabolism and hormonal changes, also play a role in determining the speed at which a person's skin ages. Instrinsic aging is often characterized by atrophy of the epidermal layer, which results in the skin becoming more susceptible to injury after minor trauma. In addition, decreased basal cell proliferation ability and a reduced number of fibroblast cells, collagen fibers, elastin fibers and mast cells in the dermis layer are also characteristic of skin aging. In the context of wound healing, fibroblast proliferation plays a key role in determining the final

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healing outcome. Fibroblasts produce collagen which is responsible for filling and regenerating damaged tissue, as well as influencing the re-epithelialization process that is essential for wound closure. Therefore, when fibroblast growth is inhibited, the potential for wound healing can also be significantly decreased, demonstrating how important the role of fibroblasts is in the skin healing process.

In wounded aging skin, the wound healing response depends on the interaction of bio-chemical and mechanical signaling cascades to coordinate the stages of hemostasis, inflammation, proliferation and remodeling. In the hemostasis phase, there is an increase in platelet aggregation response to collagen, resulting in a decrease in bleeding time. The inflammatory phase of wound healing has reduced leukocyte concentration values due to decreased macrophage function. Proliferation phase, there is a decrease in proliferation potential during wound healing due to the influence of the structure and mechanical function of skin aging and inhibiting migration potential through the maintenance of extracellular matrix structures. There are epidermal keratinocytes that undergo the aging process and dermal fibroblasts, decreased Extracelullar Matrix (ECM) deposition and increased Matrix Metalloproteinase (MMP) activity which causes inadequate tissue tension that inhibits wound healing. In the remodeling phase, scar tissue develops with weak mechanical strength due to reduced collagen deposition by fibroblasts due to stiffness of aging skin.(2,7,8)

The wound healing process can be assisted by using Aloe Vera. Aloe vera is a plant native to Africa, a class of Liliaceae. Aloe vera consists of 300 species. The commercial species of the genus Aloe are Aloe barbadansis, Aloe perryl and Aloe ferox. Aloe barbadansis species has the highest potential as a pharmaceutical raw material. Secondary metabolite identification research of Aloe vera extract content obtained anthraquinone content, tannins, flavonoids, terpenoids, saponins (6,9,10).

Anthraquinones help protect the skin, heal wounds, and promote angiogenic growth. Anthraquinones are antibacterial agents that inhibit bacterial sugar dehydrogenation and oxidation and metabolic intercedes, as well as protein and nucleic acid production.(9,11,12) Anthraquinones contain aloesin, aloin and emodin. A lot of aloin content is found in the yellow layer, which is located between the skin and leaf flesh and a little in the flesh of the aloe vera leaf which is often associated as a wound healer.(13-15)

Research on aloin is still very limited compared to aloe vera. Research states that aloin can improve wound healing by increasing angiogenesis and fibroblast proliferation through increased expression of Fibroblast growth factor (FGF). Aloin makes skin collagen fibers more regular after healing, minimizing scarring.(11) Donkor et al, 2020 stated that aloin has inhibition against the growth of pathogenic bacteria in the skin.(14) Li et al, 2017 stated that aloin accelerates fibroblast migration thereby accelerating the wound healing process.(16) Renuga, 2019 stated that aloin has the potential as a skin tonic and accelerates the wound healing process(17).

Building upon the foundational rationale elucidated above, the researcher endeavors to delve into a comprehensive exploration aimed at elucidating the impact of aloin administration on the intricate dynamics of the wound healing process observed in male white rats undergoing aging. This investigative pursuit seeks to unravel the nuanced interplay between aloin supplementation and the wound healing trajectory in male white rats, particularly focusing on the modulation of fibroblast populations at distinct time points during the healing continuum, specifically on days 7 and 14 post-incision.

The overarching objective of this inquiry is to meticulously assess and compare the abundance and activity of fibroblasts within the incision sites of male white rats subjected to aloin administration against those subjected to standard wound healing protocols, thereby discerning any discernible patterns or alterations in fibroblast proliferation and functionality attributable to aloin supplementation. Through meticulous observation and quantification of fibroblast dynamics at these designated time intervals, this study aspires to ascertain the temporal evolution and significance of fibroblast growth in response to aloin administration amidst the aging process.

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By meticulously scrutinizing the fibroblast response within the context of aging-associated wound healing, this research endeavors to shed light on the mechanistic underpinnings and potential therapeutic implications of aloin supplementation in augmenting the regenerative capacity of aging skin. Ultimately, this study aims to contribute valuable insights into the optimization of wound healing strategies tailored to meet the unique needs of aging populations, thereby advancing the forefront of translational research and clinical practice in the realm of wound care and regenerative medicine.

2. Methods

This research is a post-test control group design research, namely data processing carried out after research treatment. In this study, data processing was carried out on day 7 and day 14. The data processed is the number of fibroblasts found in each sample.

The research sample used male white rats (Rattus norvergicus). The inclusion criteria for male white rats used are six-month-old rats with a body weight of 500-600gr. Male white rats are healthy and active during the treatment given. The exclusion criteria in this study are if the male white rats experience infection during the treatment given. The sample amounted to 24 rats which were divided into 4 groups. Each group amounted to 6 rats. The division of research groups is as follows:

- Negative control group (K-): rats were given an injury and treated with NaCl 0.9%.
- Positive Control Group (K+): rats were given a wound and treated with povidone iodine 10%.
- Treatment Group (P1): rats were given a wound and applied Aloin at a concentration of 1.25 mg.
- Treatment Group (P2): rats were wounded and applied Aloin concentration of 1.25 mg.

` Male white rats were acclimatized for 1 week, then wounded with a 4 cm x 5 cm x 0.2 cm wound incision. Rats that have been wounded will be given therapy according to the group once a day. On day 7 and day 14, fibroblast assessment will be carried out by taking rat skin tissue in the wound area.

Fibroblast assessment was performed on days 7 and 14 of aloin treatment. Fibroblast data was processed using normality test and significance test, conducted by repeated measure test followed by Bonferonni post-hoc test. The hypothesis in this study, namely:

- H0: There is no effect of Aloin administration on the increase of fibroblasts in the process of wound healing in Male white rats (Rattus norvegicus) with aging process.
- H1: There is an effect of Aloin administration on the increase of fibroblasts in the wound healing process in Male white rats (Rattus norvegicus) with the aging process.

3. Results And Discussions

Based on the data obtained, the results of the number of fibroblasts on day 7 in the healing process of incision wounds in male rats (rattus norvegicus) with the aging process after giving Aloin Extract Day 7 in this study with the following description of the results.

Fibroblast Expression on Day 7 Post Injury

The results found that on day 7 the number of fibroblast cells was highest in the control + group compared to control-P1, and P2 which can be seen in the following

Table 1. Average Fibroblasts on day 7

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Kelompok	N	Mean ± Standar Deviasi	Nilai Min	Nilai Max
K (-)	**6**	5,72±1,80	**3**	**27**
K (+)	**6**	6,55±2.57	3,67	10.67
P1	**6**	5,83±2,73	3,33	**10,67**
P2	**6**	4,44±1,02	**2,67**	**5,67**

In the affected tissue, nearby fibroblasts will proliferate, migrate and produce a large amount of collagen matrix that helps repair tissue damage. As the wound healing process is underway, fibroblasts become more hypertrophied and more basophilic, the size of the golgi complex becomes larger and the endoplasmic reticulum becomes wider. Fibroblasts begin to appear in the wound area 3 days after tissue laceration occurs.(1,18)

These results are reinforced by the research of Landen et al in 2016 which found that fibroblasts will migrate to the wound area and actively proliferate and the number of fibroblast cells begins to increase on day 3 and will continue to increase on day 5 until it reaches its peak on day 7 and becomes the dominant cell (19,20).

Based on the results of the study, the number of fibroblasts on day 7 is fibroblasts that are expressed in aging skin. This is because wound healing in aging skin has decreased the number of fibroblast cells, thus slowing down wound healing. This is in accordance with research, that in aging skin there is a decrease in fibroblast proliferation which causes a slowdown in wound healing.(4,21)

Skin aging is a combination of three processes, including decreased proliferation ability of skin cells, decreased synthesis of skin extracellular matrix, and increased activity of collagen-degrading enzymes in the dermis. Skin cells, including keratinocytes, fibroblasts and melanocytes decrease in population as we age. The decrease in fibroblast cell population leads to a decrease in collagen biosynthesis in the dermis layer.(16,22)

Based on the results of the study, although the average K + is higher than the treatment group, it has the same maximum value as P1. This shows that aloin has potential in wound healing even though on day 7 the average number of fibroblasts after being given aloin is not higher than the other groups. This is in accordance with previous research by Liang et al. 2020 in his research found that aloin can increase angiogenesis and proliferation of fibroblasts by inducing the expression of epidermal growth factors, thereby accelerating wound healing. (23).

Liu et.al research in 2015 that aloin increases fibroblasts through antioxidant activity, namely by inhibiting oxidative stress on cells due to the accumulation of free radicals, besides that aloin increases the level of gluthation which has the effect of accelerating wound healing.(15) This is in accordance with previous research stating that aloin accelerates wound healing by accelerating fibroblast migration by increasing collagen fibers so that later it will inhibit scar formation.(15)

Aloin has a function as an antioxidant that functions in wound healing.
Based on previous research by Marphirah in 2018 that biduri flowers contain flavonoids that can increase fibroblasts and accelerate wound healing due to. Flavanoids are equivalent to aloin which functions as an antioxidant (24,25).

Fibroblast Expression on Day 14 Post Injury

The results showed that on day 14 the number of fibroblasts was more in treatment group 2 than the three groups, so it can be interpreted that the administration of aloin can increase fibroblasts in the wound healing process. The results of the study can be seen in table 2.

Tabel 2. Rerata Fibroblas pada hari ke-14

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Kelompok	N	Mean ± Standar Deviasi	Nilai Min	Nilai Max
K (-)	**6**	5,33±1,56	**3,33**	**7,67**
K (+)	**6**	5,05±1.06	3,33	**6**
P1	**6**	5,44±0,88	**4**	**6,33**
P2	**6**	6,10±1,32	**4,33**	**8,33**

Kumar and Yadav, 2014 stated that aloin functions as a wound healer(26). Aloin can promote wound healing by increasing angiogenesis and fibroblast proliferation through increased EGF expression. Aloin can make skin collagen fibers more regular after healing, minimizing scarring and aloin also protects the skin by reducing lipid peroxidation and reactive oxygen species while increasing SOD and glutathione peroxidase activity.(11,14)

The process of wound resurfacing with new epithelium or re-epithelialization with fibroblast migration and proliferation has an important role in the normal healing process. In aging skin, decreased signaling to fibroblasts also leads to a decrease in collagen formation by reducing the secretion of monocyte chemoattractant protein-1 (MCP-1) and a resulting decrease in inflammatory chemotokine pathways that regulate fibrosis as well as a decrease in the mechanical strength of scars with aging skin. The remodeling process is the stage of tissue formation with optimal or better shape, size and strength.(2,27)

Based on the results of the study on day 14, the K + group experienced a decrease in fibroblasts because they will enter the remodeling or maturation phase which aims to form new tissues. However, the wound closure is not better than aloin because in aging skin there is an obstacle to collagen formation which affects the process of forming new tissues and is caused by povidone iodine which has toxic substances so that it hinders the process of forming new tissues and causes scabs. Povidone iodine has toxic properties on fibroblasts that interfere with collagen activity in forming new tissues and the accumulation of iodine so that it forms a thicker scab (28). The results of the study on day 14 that were seen macroscopically were that the wounds given aloin could close the wounds better than the control group. This is due to the ability of aloin to form new tissue better..

Giving aloin contained in Aloe vera because it has been proven to increase the number of fibroblasts. Fibroblasts are an important component in the wound healing process, especially in the proliferation phase. Fibroblasts will produce collagen, then collagen will contract so that the edges of the wound will interlock until the wound heals and returns to its original state.(5) In addition, aloin also makes skin collagen fibers more regular after fibroblast healing so as to reduce scar formation, aloin also inhibits the inflammatory response.(23)

Effect of Aloin Administration on the Increase of Fibroblasts

The normality test of data in each group is normally distributed so that the bivariate significance test performed is a repeated measure test. In the significance test, the p value> 0.05 was obtained so that H1 was rejected. The significance test was continued to the Bonferonni test as a post-hoc. In the Bonferonni test, it was found that there was a significant increase in fibroblasts in treatment group 2. The test results are shown in tables 3 and 4

Tabel 3. Uji Signifikansi dengan *Repeated measure test*

Kelompok	N	*Normality test*	p	Bonferonni

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K (-)	**6**	normal	**0,582**	
K (+)	**6**	normal		
P1	**6**	normal		**0,000**
P2	**6**	normal		

Based on research even though Ha is rejected, the administration of aloin can improve post-wound scar and can increase fibroblast cells in wound healing as evidenced in the results of the study. In accordance with the theory which states that aloin also makes skin collagen fibers more regular after fibroblast healing so as to reduce scar formation, aloin also inhibits inflammatory responses.(23)

In this experiment, two mechanisms of aloin were used, namely at a low dose of 1.25 mg/ml and a high dose of 2.5 mg/ml. Based on the results of the study, it appears that the increase in fibroblasts is most effective by large doses between days 7 to 14 compared to small doses. On day 7 aloin with low dose has more fibroblasts than high dose. On day 14 aloin with a higher dose showed an increase in fibroblasts which was more than the lower dose even though on day 7 the higher dose had fewer fibroblasts. In treatment group 2 using a dose of 2.5 mg/ml compared to the treatment of 1.25 mg/ml.

The use of aloin at a dose of 2.5mg/ml is based on the results of previous research by Donkor et al in 2020 that this dose is effective in healing wounds by fighting wound pathogenic microorganisms (29). However, in this study, aloin at a dose of 1.25 mg/ml still has the effect of increasing fibroblasts in aging skin..

The results of research by Andri et al in 2019 found that significant results at all concentrations showed that the administration of low doses of aloe vera (Aloe vera L.) was able to have an effect on increasing the number of fibroblast cells. The more concentration of aloe vera (Aloe vera L.) received by the injured skin, the more active substance content will be received. So that in the treatment of giving aloe vera juice (Aloe vera L.), the graph of the number of fibroblast cells increases from the lowest to the highest concentration. This is because the more active substances are absorbed, the more stimulus is received. This proves that the theory regarding the active substance (aloin) in aloe vera (Aloe vera L.) is able to increase the number of fibroblast cells in accordance with the results of the research obtained.(30)

Based on the study of the number of fibroblasts on day 14 in the treatment group there were more fibroblasts than the positive control group, but lower on day 7 than the positive group. The difference in the number of fibroblasts between groups indicates that the aloin treatment group has increased fibroblasts so that it can help the wound healing process..

4. Conclusions

This study undertakes a comprehensive investigation into the therapeutic potential of aloin extract in facilitating the wound healing process in aging male white mice, employing rigorous and meticulous scientific methodologies. Through a systematic and detailed experimental approach, the research uncovers intriguing insights into how tissues respond to the treatment with aloin extract, particularly focusing on its impact on the modulation of fibroblast cell populations.

Fibroblasts, recognized as pivotal players in the wound healing cascade, are instrumental in orchestrating the synthesis and deposition of extracellular matrix components crucial for the structural restoration of damaged tissues. Through extensive analysis, the study unveils that aloin extract possesses the capability to expedite tissue regeneration by promoting fibroblast proliferation, thereby augmenting the production of collagen and critical growth factors pivotal for wound repair and regeneration.

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A noteworthy aspect of this investigation is the discovery that the stimulatory effect of aloin extract on fibroblast proliferation mirrors the response elicited by povidone iodine, a widely utilized antiseptic agent in clinical settings. These findings not only affirm the efficacy of aloin extract in facilitating the wound healing process but also provide deeper insights into its mechanistic underpinnings, potentially paving the way for the development of more sophisticated wound healing modalities.

Significantly, this study serves as a catalyst for the advancement of more efficacious and targeted treatment modalities aimed at accelerating wound healing, particularly among populations characterized by diminished skin regenerative capacities due to aging or specific medical conditions. Given the intricate biological dynamics of wound healing and its clinical implications, these findings lay a robust groundwork for translational research endeavors aimed at seamlessly integrating scientific advancements into clinical practice, thereby offering pertinent and advantageous interventions for patients in need.

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