The Efficacy of Catfish Skin Gelatin (*Pangasius djambal*) on Soft Tissue Healing of the *Rattus norvegicus*

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ABSTRACT

Background: *Traumatic ulcers are common oral mucosal lesions causing discomfort, infection, and delayed healing. of Pangasius djambal fish skin gelatin was chosen as a bioactive component because it is a natural biomaterial rich in amino acids, which play a role in regulating inflammation and tissue regeneration, particularly in influencing the number of macrophages and lymphocytes in the inflammatory phase and fibroblast proliferation. The primary objective was to determine the effect of Pangasius djambal fish skin gelatin on the healing process of traumatic ulcers.*

Method: *Research subjects were divided into three main groups based on treatment and further divided by the day of tissue collection. Tissue samples were collected on days 3, 5, and 7, followed by hematoxylin-eosin (HE) staining to observe macrophages, lymphocytes, and fibroblasts under a microscope using 400× magnification.*

Result: *Statistical analysis using the One-way ANOVA test showed a significant difference ($p < 0.05$) in the number of macrophages, lymphocytes, and fibroblasts across all experimental groups. In the treatment group receiving 100% Pangasius djambal skin gelatin, a significant decrease in macrophages and lymphocytes was observed on 5th and 7th days, indicating a faster resolution of the inflammatory phase. Simultaneously, there was a significant increase in the number of fibroblasts from the 5th to the 7th day in the treatment group compared to the control group, demonstrating accelerated granulation tissue formation and enhanced wound healing.*

Conclusion: *The recovery of traumatic ulcers in Rattus norvegicus can be affected by the application of Pangasius djambal skin gelatin.*

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INTRODUCTION

Traumatic ulcer Common oral lesion, such as traumatic ulcers, have a higher prevalence compared to other oral lesions. The prevalence rate of traumatic ulcers in the world is as high as 25%[1]. Traumatic ulcers are frequently found on buccal mucosa (42%), the tongue (25%), and the lower labial mucosa (9%)[2]. This lesion is a self-limiting disease that can heal within 7-14 days. This lesion can be caused by mechanical, thermal, or chemical trauma, which can cause discomfort, infection, and delayed healing[3,4]. The process of healing traumatic ulcers requires coordination between cytokines, immune cells, inflammatory mediators, and other tissue repair mechanisms[5]. The soft tissue healing process includes the Inflammatory Phase, which began immediately upon injury and usually lasts 3-4 days, the Proliferation Phase, which begins between day 3 and 5, the Maturation Phase, and the Remodeling Phase[6,7].

In the healing process of soft tissue wounds, macrophages, lymphocytes, and fibroblasts are part of the inflammatory response that is present within 48-96 hours and peaks on the 3rd day. Macrophages perform various functions, ranging from host defense, controlling inflammation, to supporting cell proliferation and tissue restoration[8]. Macrophages act as an essential role in both the early and late stages, including in the healing of traumatic ulcers. These cells act through phenotypic changes that regulate the change from the inflammatory to the remodeling phase[5].

Lymphocytes originate from lymphoid progenitor cells, which are part of the adaptive immune system. In the wound healing process, lymphocytes provide a specific response to microbes and other foreign objects present in the wound. The number of lymphocytes increases during inflammation, causing activated macrophages to release cytokines. This increase in cytokine levels can prolong the inflammatory phase. If the inflammatory phase lasts too long and the number of lymphocytes continues to increase, this can cause tissue damage. T lymphocytes are the most common type of lymphocytes found during the wound healing process because they have the ability to regulate the cellular response to injury. In addition, these lymphocytes can also direct inflammatory and fibrotic factors in wounds towards a better regenerative process[9].

Fibroblasts are connective tissue cells that play a major part in the wound healing process, especially in the proliferation phase, through cell migration, proliferation, and collagen synthesis as primary part of the extracellular matrix[10]. An enhance number of fibroblasts reflects the formation of granulation tissue and collagen deposition, which contribute to tissue regeneration, particularly in traumatic ulcers[11]. Therefore, the number of fibroblasts is often used as a histopathological parameter to assess the effectiveness of topical agents in accelerating the wound healing process[12].

To achieve optimal healing, conventional therapies which include antiseptics, topical steroids, and antibiotics are typically employed yet these effective conventional treatments may lead to complications like antibiotic resistance, paving the way for research into economical and biological alternatives like natural polymers[5]. Therapies derived from herbal materials that are not only safe, effective, and possess biological capabilities in supporting tissue regeneration but are also economical are expected to serve as alternative therapies to support optimal healing in traumatic ulcers [13–15].

One alternative therapy that can be used is gelatin. Along with the development of biomaterial research, gelatin has become an interesting material for further study. Gelatin is a natural polymer made from the hydrolytic degradation of collagen protein, and its unique amino acid structure provides several medical benefits.

As a source of gelatin protein matrix, collagen is the most abundant protein found naturally in humans and animals[16].

One of a kind animal that can be used to produce gelatin is catfish because it contains 68.6% protein[15]. Catfish skin gelatin (*Pangasius djambal*) has been proven to be superior to other types of fish skin gelatin[6]. Gelatin extracted from fish scales and skin is a biopolymer containing 85% to 92% protein, mineral, and water[16]. Catfish skin is considered environmentally unfriendly waste. Fish skin is solid waste produced by the fish processing industry that has no use or added value[14]. Although products derived from catfish are quite popular with the public, innovation in their use is still very limited. This can be an opportunity in pangasius fish processing, which has various health benefits[17].

Previous studies have shown that catfish skin gelatin (*Pangasius djambal*) can increase the number of lymphocytes and macrophage cells, as well as increase the expression of ALP, TNF, RUNX2, OPG, STAT-3, and EGF after tooth extraction in white rats (*Rattus norvegicus*). Another study also showed that catfish skin gelatin at a certain concentration can reduce the expression of RANK and RANKL, which when bound together cause osteoclast differentiation and proliferation, resulting in bone resorption.

Research by Mardiyantoro et al., 2019 showed an increase in the number of fibroblasts in wounds after tooth extraction in white rats (*Rattus norvegicus*) that were given catfish skin gelatin (*Pangasius djambal*)[18]. A number of studies have proven the positive effects of *Pangasius djambal* fish skin gelatin on wound healing parameters such as the number of fibroblasts and the expression of bone healing proteins, but no studies have specifically examined its effect on wound healing in soft tissue, especially the oral mucosa. In fact, macrophages are key cells in modulating inflammatory responses and tissue regeneration. Based on the above description, this study was conducted to determine the effect of catfish skin gelatin (*Pangasius djambal*) administration on the healing process of soft tissue in the oral cavity of white rats (*Rattus norvegicus*).

RESEARCH METHOD

This study employed a true experimental design in a laboratory in vivo using a Randomized Post Test Only Controlled Group Design. A total of 36 male Wistar rats (*Rattus norvegicus*) were used as research subjects and divided into three main groups based on the treatment; the Negative Control (NC) group, which was given ulceration without medication; Positive Control (PC) groups, which was treated using Aloclair Plus Gel™ on traumatic ulcers; and Treatment (T) groups, which was treated using 100% concentration of pangasius catfish skin gelatin on traumatic ulcers. Each group was further subdivided based on the day of tissue collection; 1 = day 3; 2 = day 5; and 3 = day 7.

This study had received ethical clearance from the Health Research Ethics Committee of the Faculty of Dentistry, Brawijaya University, with number 053/UN10.F1301/KEPK-FKGUB/EC07/2025 for using animal as a subject. The research subjects used in this study were male Wistar strain white rats (*Rattus norvegicus*) kept in the Animal House of the Faculty of Dentistry, Brawijaya University. They were kept in clean and well-maintained cages. In this study, a minimum of 3 white rats were used for each group. This study was divided into three main groups based on the treatment and further subdivided based on the day of tissue collection forming a total total of 9 groups, which required 27 white rats. To reduce sample loss due to rat mortality, the number of samples was increased by one in each group, bringing the total to 36 white rats.

Preparation of *Pangasius djambal* Skin Gelatin

Pangasius catfish skin gelatin was obtained from pangasius catfish (*Pangasius djamba*l) skin using a commercial technique without drying, with a concentration of 100%. *Pangasius djambal* skins were thawed, and cut into small pieces 1 x 1 cm^2. Gelatin extracted by immersing the *Pangasius djambal* skin in citric acid with pH = 3 mixture with a ratio of 1:4 (w/v) at room temperature for 12 hours. Subsequently, the skin are rinsed using flowing water until the pH returns to normal (pH = 7). Futhermore, the swollen skin are extracted with aquadest, in a water bath (at 90°C) with a ratio of 1:3 (w/v) for two hours. Thereafter, the filtrate collected by straining with Wathman paper number 1. Last, the gelatin was cooled down to room temperature until a gel forms and sterilized using UV light for 30 minutes[19].

Traumatic Ulcers Induction

Traumatic ulcers were created on the *Rattus norvegicus* mucosa by applying thermal trauma. The rat's labial mucosa will be induced with heat by applying the hot cement stopper with a diameter of ± 2 mm for 3 seconds. On the second day, observe the ulcer, which is characterized by a round, white lesion with a yellowish center containing fibrinous exudate and red edges. After the ulcer formed, treatment was administered to each group[20].

Ulcers Medication

Catfish skin gelatin and Aloclair Plus Gel™ were applied to the traumatic ulcer on the labial mucosa of the rats. The medication were administered once after the ulcer formed on the labial mucosa of the white rats at a dose of 0.1 ml catfish skin gelatin, while the PC group was given Aloclair Plus Gel™ at a dose of 0.1 ml, and the NC group received no treatment.

Tissue preparation

On days 3, 5, and 7 after thermal induction and gel application, each treatment group was euthanized in accordance with the treatment group by cervical dislocation, and the lower jaw labial mucosa tissue was collected. After collecting the lower jaw labial tissue and fixing the tissue, the tissue was then processed with an Automatik STP120 Thermo device and sliced using a rotary microtome with a thickness of 3 microns. The next step was staining with hematoxylin eosin using a Tissue Tek®DRS™ device.

Statistical Analysis

Observations were made to observe the number of macrophages, lymphocytes, and fibroblasts per field of view in histopathological preparations made with hematoxylin eosin staining. Macrophages, lymphocytes, and fibroblasts were counted using an Olympus microscope and OlyVIA software at 400x magnification. The preparations were then photographed per field of view and viewed on a monitor screen. The number of macrophages, lymphocytes, and fibroblasts was counted in 3 fields of view and the average was calculated for each sample.

Based on the research conducted, an overview of inflammatory cell infiltration around the granulation tissue area of traumatic ulcers was obtained, as written by Suryana *et al*. (2023) that traumatic ulcers show inflammatory cell infiltration on histopathological evaluation[21]. The inflammatory cells involved are macrophages, lymphocytes, and fibroblasts. Macrophages stained with Hematoxylin Eosin appear oval, round, or kidney shaped with vacuolated cytoplasm and a round, purple-colored nucleus. The size of the macrophages found varies from medium to large[13]. Meanwhile, lymphocytes with Hematoxylin Eosin staining are identified based on the morphology of large round nuclei with a blue-purple color that almost fills the cell cytoplasm[21].

Fibroblasts in Hematoxylin eosin staining appear as elongated nuclei surrounded by a smooth membrane with one or two clearly stained purple-blue nucleoli[10,22].

Data in the form of the average number of macrophage, lymphocyte, and fibroblast cells on each sample were averaged per group, then statistically analyzed using statistical data processing software with a confidence level of 95% (α = 0.05) and a significance level of 0.05 (p = 0.05).

RESULTS

Results and Data Analysis of Macrophage

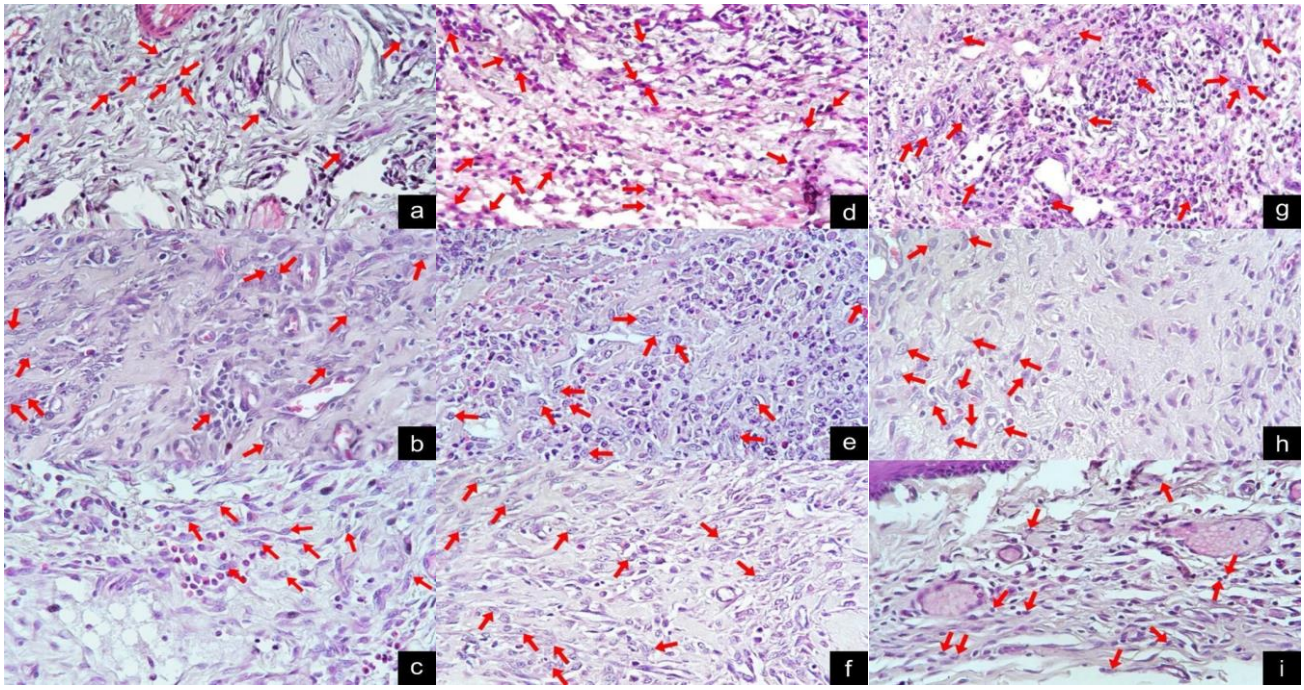

Figure 1. Histological description of macrophages in traumatic ulcers of *Rattus norvegicus* using Hematoxylin Eosin staining with 400x magnification on a) NC1, b) NC2, c) NC3, d) PC1, e) PC2, f) PC3, g) T1, h) T2, i) T3.

Table 1. Average Number of Macrophage Cells in Traumatic Ulcers of *Rattus norvegicus*

Group	Macrophages
NC1	11,667 ± 0.333
PC1	22,111 ± 1.018
T1	18,222 ± 0.509
NC2	12,667 ± 0.333
PC2	15,333 ± 0.333
T2	13,667 ± 0.333
NC3	11,222 ± 0.509
PC3	12,333 ± 0.333
T3	11 ± 0.333

Note: The numbers listed in the table represent the mean number of cells ± SD.

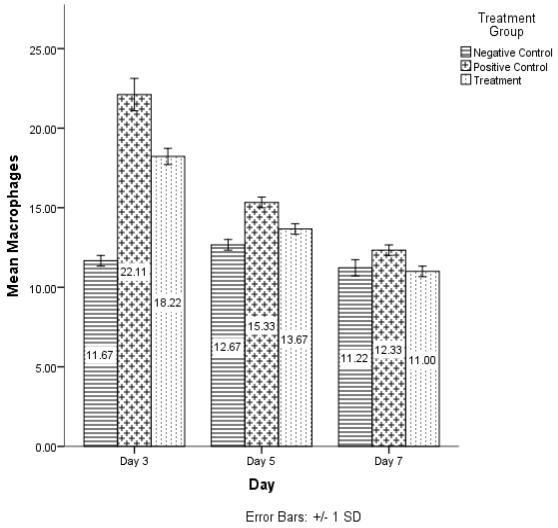

Figure 2. Graph of the Average Number of Macrophage Cells in Traumatic Ulcers of *Rattus norvegicus* in the Control and Treatment Groups.

According to Table 1, the number of macrophage cells between the control group without *Pangasius djambal* skin gelatin administration and the treatment group given *Pangasius djambal* skin gelatin shown a difference. The p-value = 0.000 ($p < 0.05$) was obtained by One-way ANOVA test, which shown a significant difference in the number of macrophage cells among the control and treatment groups, and a decrease in macrophages was observed on days 5 and 7. A significant difference in the mean number of macrophages among groups The Post Hoc LSD test also obtained with a p-value < 0.05. However, there were still some group comparisons that showed a p-value > 0.05, namely NC1 with NC3 and NC3 with P3.

Results and Data Analysis of Lymphocytes

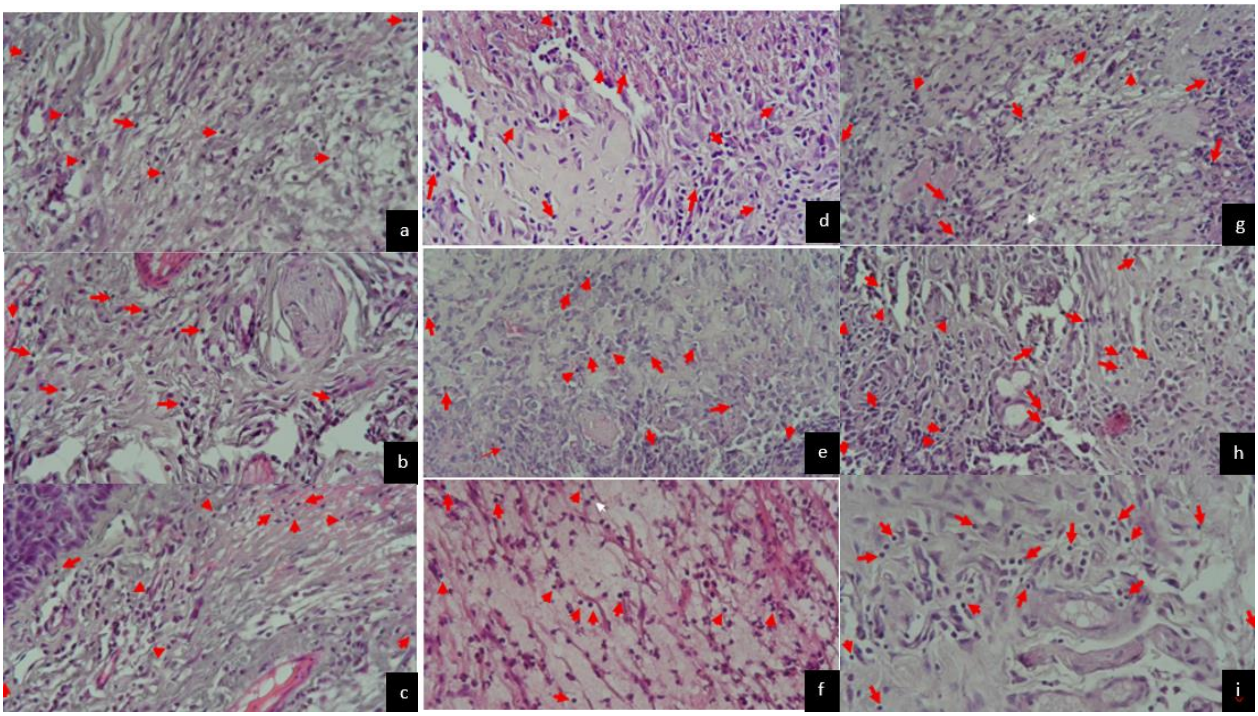

Figure 3. Histological description of lymphocytes in traumatic ulcers of *Rattus norvegicus* using Hematoxylin Eosin staining with 400x magnification on a) NC1, b) NC2, c) NC3, d) PC1, e) PC2, f) PC3, g) T1, h) T2, i) T3.

Table 2. Average Number of Lymphocytes in Traumatic Ulcers of *Rattus norvegicus*

Group	Lymphocytes
NC1	26,557 ± 1.555
PC1	22,111 ± 2.018
T1	15,111 ± 2.018
NC2	18,556 ± 1.555
PC2	14,333 ± 1.555
T2	11,222 ± 1.305
NC3	14,222 ± 1.555
PC3	9,555 ± 1.555
T3	6,555 ± 1.010

Note: The numbers listed in the table represent the mean number of cells ± SD.

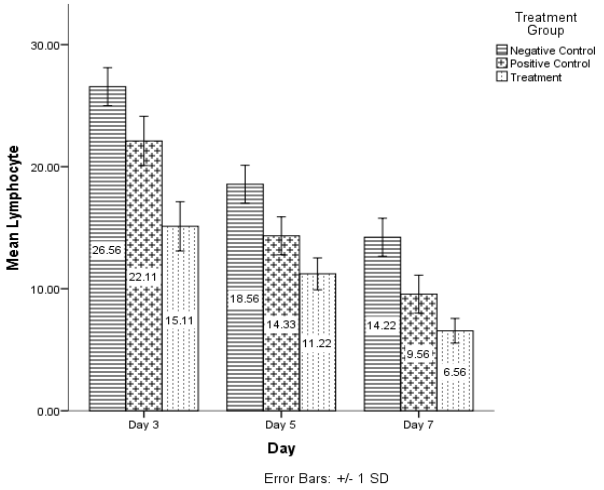

Figure 4. Graph of the Average Number of Lymphocytes in Traumatic Ulcers of *Rattus norvegicus* in the Control and Treatment Groups.

Data Analysis Based on Table 2, variations in lymphocyte cell counts were identified among the NC group and the T group that received *Pangasius djambal* fish skin gelatin intervention. A significance value of p = 0.000 (p < 0.05) was obtained based on statistical analysis using the One-way ANOVA test, providing strong evidence that in the number of lymphocytes between the control group and the treatment group has significant difference, accompanied by a decrease in lymphocyte density observed on the 5th and 7th days. In addition, Post Hoc LSD test also confirmed a significant difference in the average lymphocyte count among the groups with a p value < 0.05. However, several correlations between groups were found to be insignificant or had p values > 0.05, namely in the comparison between the NC1 and T1 groups and between the PC3 and T3.

Results and Data Analysis of Fibroblast

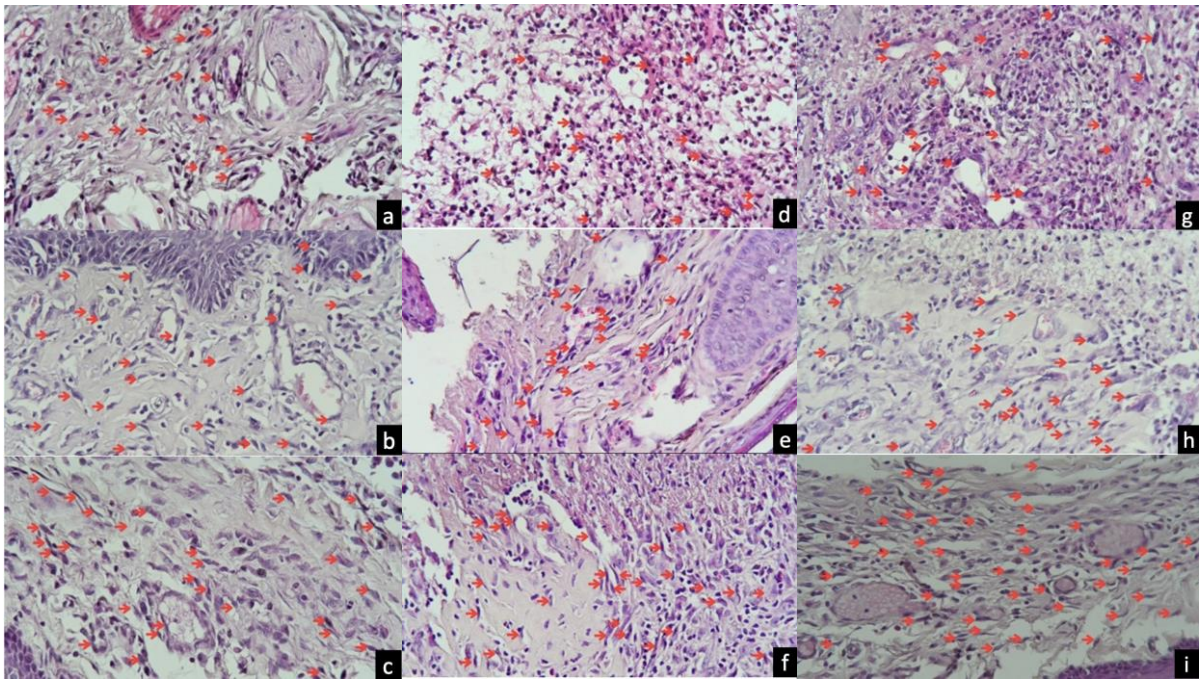

Figure 6. Histological description of Fibroblast in traumatic ulcers of *Rattus norvegicus* using Hematoxylin Eosin staining with 400x magnification on a) NC1, b) NC2, c) NC3, d) PC1, e) PC2, f) PC3, g) T1, h) T2, i) T3.

Table 3. Average Number of Fibroblast Cells in Traumatic Ulcers of *Rattus norvegicus*

Group	Fibroblast
NC1	19.7 ± 1.414
PC1	20.67 ± 2.494
T1	24.00 ± 2.700
NC2	22.23 ± 2.358
PC2	25.70 ± 1.000
T2	29.70 ± 1.650
NC3	26.67 ± 1.527
PC3	32.00 ± 0.700
T3	40.9 ± 0.721

Note: The numbers listed in the table represent the mean number of cells ± SD.

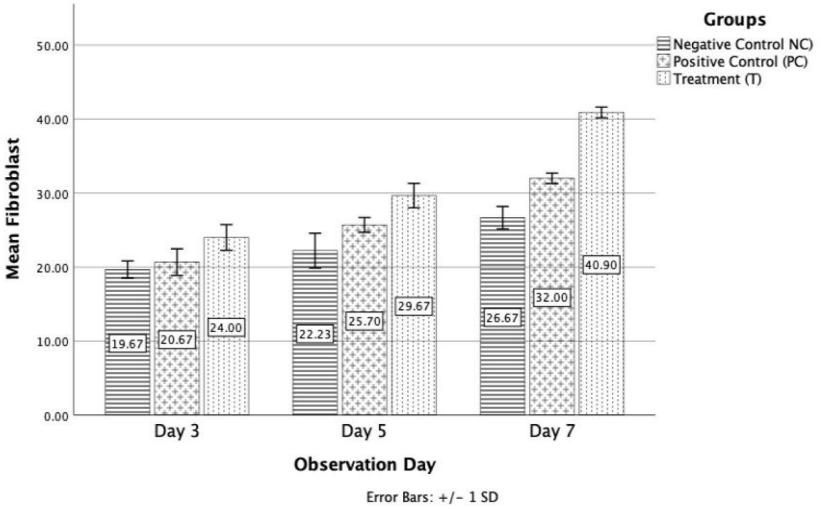

Figure 6. Graph of the Average Number of Fibroblast Cells in Traumatic Ulcers of *Rattus norvegicus* in the Control and Treatment Groups.

Data Analysis Based on Table 3, the number of fibroblast cells between the control group without *Pangasius djambal* skin gelatin administration and the treatment group given *Pangasius djambal* skin gelatin have a significant difference. A result of p-value = 0.000 ($p < 0.05$) obtained using the One-way ANOVA test, which means the number of fibroblasts between the control and treatment groups have a significant difference. Descriptively, there was an enhancement in the number of fibroblasts over time, especially on 5th and 7th days. A significant difference in the mean number of fibroblasts between groups also obtained by Post Hoc LSD test with a p value < 0.05. However, there were several group comparisons that show no significant difference ($p > 0.05$), namely between NC1 and PC1 and PC1 and T1.

DISCUSSION

Macrophage, lymphocyte, and fibroblast cells were counted and compared among treatment groups. The average number of macrophages, lymphocytes, and fibroblasts involved two independent factors, namely the treatment group and the day of observation, so to determine the effect of each factor and their interaction on the number of macrophage, lymphocyte, and fibroblast cells, a two-way ANOVA test was used. Based on the results of the Two-way ANOVA test, it was found that the treatment group factor had a significant effect on the number of macrophages, lymphocytes, and fibroblasts, as did the observation day factor. In addition, there was a significant interaction among the treatment group factor and the observation day. This indicates that the effect of treatment on the number of macrophages, lymphocytes, and fibroblasts depends on the observation day.

To observe the effect of treatment on the average number of macrophages, lymphocytes, and fibroblasts based on the day of treatment, a One-way ANOVA test was performed. Based on the One-way ANOVA test, there were significant differences in the average number of macrophages on 3rd, 5th, and 7th days in the NC group, PC group, and T group. This indicates that the administration of catfish (*Pangasius djambal*) skin gelatin affects the average number of macrophages in traumatic ulcers in white rats.

On the Post Hoc LSD test results, the number of lymphocytes in the NC group showed no significant differences on 3rd, 5th, and 7th days, which in this study reflects the natural course of the inflammatory phase without external therapeutic intervention. This condition is in line with studies stating that traumatic ulcers characteristically trigger a strong immune response with massive infiltration of inflammatory cells as an initial defense of the tissue against injury. Without the application of active ingredients that accelerate inflammation resolution, adaptive immune cells such as lymphocytes will remain concentrated in the wound area to regulate pro-inflammatory cytokines, resulting in a slower healing process compared to the treated group[23].

Meanwhile, the Post Hoc LSD test of the number of fibroblasts in the NC group showed no significant difference on 3rd day. This indicates that in the early inflammatory phase, fibroblast proliferation has not yet occurred optimally because the wound healing process is still dominated by inflammatory cell activity, while growth mediators that stimulate fibroblast migration and proliferation have not increased significantly. On 5th and 7th days, the number of fibroblasts in the NC group increased, reflecting the transition to the physiological wound healing proliferation phase without therapeutic intervention.

Meanwhile, the PC group had the highest number on 3rd day and experienced a significant decrease on 5th and 7th days. This is in accordance with research that was conducted by Indraswary et al., 2022, which found that aloe vera activates macrophages for proliferation, causing their number to increase on 3rd day and

supported by research conducted by Dewi et al., 2024, which states that Aloclair Plus Gel™ contains polyvinylpyrrolidone (PVP) as a mucoprotector, which protects the nerve endings in the mucosa so that it can prevent irritation, and also contains hyaluronic acid and aloe vera which help the natural healing process[24].

Statistically, through a Post Hoc test, on the 3rd day shows no significant difference in the PC group. This indicates that although Aloclair Plus Gel™ is effective in providing mucosal protection through the formation of a protective layer, this material does not directly intervene in or modulate the cellular immune response. This phenomenon reinforces the notion that lymphocyte migration to the wound site is part of the adaptive immune response that will continue according to its physiological duration unless there is an active immunomodulatory agent capable of accelerating the shift from the inflammatory phase to the proliferation phase[25]. Unlike on 3rd, 5th and 7th days, a significant difference was shown in the PC group. On 5th day, the wound physiologically enters the transition phase from inflammation to proliferation. This phase is characterized by a decrease in inflammatory cell infiltration and an increase in fibroblast mitotic activity, collagen synthesis, and angiogenesis[26].

In fibroblasts, there were no significant differences between 3rd and 5th days, while on 7th day the number of fibroblasts was significantly increasing. This indicates that materials containing PVP and sodium hyaluronate play a role in forming a bioadhesive layer on the ulcer surface, maintaining mucosal moisture, and protecting tissues from mechanical and chemical irritation, thereby functioning more in stabilizing the wound environment than in directly stimulating fibroblast proliferation. This condition is supported by research conducted by Kapoor et al. (2011), which states that PVP and sodium hyaluronate support physiological wound healing through the formation of a protective barrier[27]. A significant increase in the number of fibroblasts on 7th day indicates that after local inflammation is controlled, a stable wound environment allows natural fibroblast proliferation to occur[25].

This study shows that catfish (*Pangasius djambal*) skin gelatin can affect the number of macrophages, lymphocytes, and fibroblasts. Arginine is one of the components in catfish skin gelatin that increases the mitogenic activity of peripheral blood lymphocytes and reduces post-traumatic damage in the lymphocyte blastogenesis process[28]. Lymphocytes release IFN-ɣ (interferon-ɣ), which affects macrophage aggregation. Macrophages then move to the wound site and function in cytokine production to activate growth factors such as TGF and FGF, which stimulate fibroblast proliferation[7]. Fibroblasts play a very important role in the repair process, namely being responsible for preparing the production of protein structures used during the tissue repair process. The glutamine content in catfish skin gelatin plays a role in increasing fibroblast cells during the proliferation process, as well as increasing the amount of collagen, so that the wound healing process can improve and wound closure will be faster. Meanwhile, glycine plays a role as a constituent of collagen and new blood vessels[18].

The treatment group showed an increase in the average number of macrophage cells on day 3 because macrophages act as an essential role in the body's defense system that triggers, suppresses, or modulates the adaptive immune response. This increase in macrophages was influenced by the arginine compound contained in catfish skin gelatin (*Pangasius djambal*) and a significant decrease on 5th and 7th day because macrophages act as phagocytic agents that undergo apoptosis and are then replaced by fibroblasts. The reduction in the number of macrophages also indicates that the healing process has entered the proliferation phase. This condition is supported by research that has been conducted by Mardiyantoro et al., 2021, found that the average

number of macrophages after tooth extraction in *Rattus norvegicus* with the administration of *Pangasius djambal* fish skin gelatin on 3rd day increased, and on 7th day, there was a significant decrease[29].

Aligned with macrophages, the treatment group have shown an increase in the average number of lymphocytes on 3rd day and continued to decline trough 7th day. On 5th and 7th day was found that the treatment group had a significant difference, indicating that the administration of pangasius skin gelatin played an active role in accelerating the decline in lymphocyte cell infiltration compared to natural healing without intervention. These findings are in line with research stating that the late proliferation phase is characterized by a drastic decrease in chronic inflammatory cells along with increased fibroblast activity and collagen synthesis for complete wound closure[26]. The significant decrease in lymphocytes in the treatment group also proves the ability of gelatin to prevent prolonged inflammation, which can inhibit healthy tissue regeneration if not treated immediately.

In fibroblasts, a significant increase on 5th and 7th day indicates that the healing process has entered the proliferation phase, while in the early phase, fibroblast activity has not yet been optimal because it is still dominated by the inflammatory response. This increase indicates the role of pangasius skin gelatin, which is rich in amino acids such as glycine and glutamine, in accelerating the transition to the proliferation phase. As a collagen derivative, gelatin functions as a temporary matrix that supports fibroblast adhesion, migration, and proliferation and stimulates collagen synthesis, thereby accelerating granulation tissue formation. This condition is supported by research conducted by Mardiyantoro et al. (2019), which states that collagen-based gelatin can increase fibroblast migration and proliferation as well as collagen synthesis in the proliferation phase of wound healing[18].

CONCLUSION

The application of *Pangasius djambal* skin gelatin significantly accelerates the healing of traumatic ulcers in the oral mucosa of *Rattus norvegicus*. The research demonstrates that the gelatin promotes more efficient transition from the inflammatory phase to the proliferation phase. It triggers an initial increase in macrophages on 3rd day to initiate healing, followed by a significant reduction in both macrophages and lymphocytes by 7th day, which prevents prolonged inflammation. Simultaneously, the gelatin significantly increases fibroblast counts starting from 5th day, which enhances granulation tissue formation and leads to faster wound closure. These effects are primarily attributed to the rich presence of amino acids such as arginine, glycine, and glutamine, which stimulate immunomodulation and collagen synthesis.

As a sustainable and cost-effective biomaterial derived from industrial fish waste, catfish skin gelatin represents a promising alternative to conventional therapies for oral mucosal lesions. Given its proven efficacy in accelerating soft tissue regeneration, future efforts should focus on human clinical trials to validate these results in a clinical setting. Additionally, the development of specialized topical delivery systems or formulations could further optimize the stability and application of this gelatin as a standardized herbal treatment in dentistry.

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