



## EFFECTIVENESS OF CHANNA STRIATA EXTRACT GEL ON WOUND HEALING IN ANIMAL MODELS

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### ABSTRACT

Wound healing is a crucial aspect in orthopedics. *Channa striata* (snakehead fish) contains albumin and other bioactive compounds thought to accelerate wound healing. To assess the effectiveness of *Channa striata* extract gel on wound healing in Wistar rats based on clinical (wound area) and histopathological (HEALS-A score) parameters. Laboratory experimental research with post-test only control group design using 27 male Wistar rats, divided into three groups: negative control (no treatment), positive control (Bioplacenton), and treatment (Vipalbumin gel). Evaluation of wound area was performed on days 0, 3, 7, and 14 using ImageJ. Histopathological examination was conducted using HE staining and HEALS-A scoring. Data were analyzed using ANOVA and Chi-Square tests. On day 14, the mean wound area of the treatment group ( $7.1 \pm 2.8$  mm<sup>2</sup>) was equivalent to the positive control ( $6.7 \pm 2.5$  mm<sup>2</sup>), both significantly smaller than the negative control ( $54.2 \pm 32.5$  mm<sup>2</sup>;  $p < 0.001$ ). HEALS-A scores showed significant differences between groups on days 3, 7, and 14 ( $p < 0.001$ ;  $p = 0.001$ ;  $p = 0.001$ ). *Channa striata* extract gel effectively accelerates wound healing clinically and histologically, with effectiveness equivalent to Bioplacenton.

Keywords: albumin; *channa striata*; wistar rats; wound healing

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## INTRODUCTION

Wound healing is a fundamental biological process and a critical determinant of clinical outcomes in orthopedics and traumatology, where musculoskeletal injuries and surgical interventions are highly prevalent. Traumatic injuries, fractures, open wounds, and operative incisions are frequently encountered in this field and often involve complex interactions between bone, soft tissue, vascular structures, and implanted materials. Unlike wounds in other clinical contexts, orthopedic and traumatic wounds are commonly associated with extensive tissue damage, contamination, ischemia, and the presence of fixation devices, all of which can significantly impair the normal healing cascade. The wound healing process is divided into several interconnected and interdependent phases leading up to the formation of new tissue. Fibroblasts are one of the cellular components and the main ingredient in collagen fiber formation. This can interfere with the wound healing process. Several factors can accelerate the healing process, one of which is nutrition. Consequently, delayed wound healing and wound-related complications remain major challenges in orthopedic practice and contribute substantially to patient morbidity and healthcare burden (Sanz-Ruiz et al., 2025). The integrity and viability of soft tissue surrounding bone structures play a pivotal role in achieving successful fracture healing and functional recovery. Adequate soft tissue coverage is essential not only for mechanical protection but also for maintaining local vascularity, oxygenation, and nutrient delivery to the injured bone. Compromised soft tissue conditions have been shown to negatively influence fracture union, increase the risk of infection, prolong hospital length of stay, and reduce overall quality of life. Furthermore, wound complications are closely associated with higher rates of

postoperative readmission, revision surgery, and long-term disability (Lei, Xiang, Chen, & Pan, 2023). Therefore, management must be holistic, addressing both soft tissue and bone simultaneously. Soft tissue complications can hinder bone healing and, conversely, can even be a major cause of additional hospitalizations and postoperative readmissions (Sanz-Ruiz et al., 2025).

Soft tissue complications, including delayed epithelialization, infection, necrosis, and excessive inflammation, can directly hinder bone healing by disrupting the local biological environment necessary for osteogenesis. The complexity and high incidence of wound complications demand the development of innovative therapies based on natural compounds to accelerate healing and reduce morbidity. Natural bioactive compounds such as turmeric, green tea, honey, garlic, aloe vera, propolis, pineapple, *Centella asiatica*, *Punica granatum*, and *Calendula officinalis* have been reported to possess biological and phytochemical activities that support wound healing (Ryall, Duarah, Chen, Yu, & Wen, 2022; Trinh et al., 2022; Yang et al., 2025).

In recent years, growing attention has been directed toward the use of natural bioactive compounds as alternative or adjunctive therapies for wound management. Numerous natural substances have been reported to possess biological, anti-inflammatory, antioxidant, antimicrobial, and regenerative properties that support various phases of wound healing. One potential natural source is *Channa striata*, or snakehead fish, which is widely found in Southeast Asia, especially Indonesia and Malaysia. This fish is rich in albumin, essential amino acids, type XI collagen, actin, and myosin (Lee, Choo, Norazit, Noor, & Shaikh, 2022; Yuliana, Sartini, Djide, & Djabir, 2022). High albumin content supports the early inflammatory phase and the formation of granulation tissue. The albumin content in this fish is a globular protein that is often used clinically to improve nutrition and the wound healing process. Albumin is used to maintain blood osmotic pressure, maintain the water content in the blood plasma, and maintain blood capacity. Furthermore, albumin also aids in the formation of body tissue, such as in wounds after surgery and burns. Albumin is the most abundant protein in plasma, accounting for approximately 60% of the total plasma volume (Ramadhanti, Sandhika, & Widodo, 2021; Yuliana et al., 2022).

Yuliana et al. (2022) reported that snakehead fish albumin reached 27.73 µg/L, which plays a role in the formation of new tissue (Lee et al., 2022; Yuliana et al., 2022). Overall, *Channa striata* has antibacterial and antinociceptive biomolecules that support tissue regeneration. Various studies support its effectiveness. Ramadhanti et al. (2021) showed that 100% extract reduced macrophages and blood vessels in wound tissue in mice, accelerating the transition to the repair phase (Ramadhanti et al., 2021). Yuliana et al. (2022) reported that a 5% transdermal patch containing snakehead fish mucus extract accelerated the healing of diabetic ulcers equivalent to positive controls on day 8 (Yuliana et al., 2022). Taslim et al. (2022) found that oral administration of *Channa striata* extract for 10 days increased serum albumin and decreased neutrophils in hyperglycemic rats with excisional wounds (Taslim et al., 2022). Despite the growing body of evidence supporting its efficacy, most existing studies on *Channa striata* have focused on oral formulations, such as extracts or supplements, while relatively few have explored its use in topical preparations. Topical delivery offers several advantages, including direct application to the wound site, higher local concentrations of active compounds, reduced systemic exposure, and potentially fewer side effects. Among topical formulations, gels are particularly attractive due to their ease of application, good patient compliance, and ability to maintain a moist wound environment, which is known to facilitate epithelialization and tissue repair. These findings indicate the therapeutic potential of *Channa striata* through anti-inflammatory, antioxidant, and increased new tissue protein synthesis mechanisms (Lee et al., 2022; Taslim et al., 2022).

This study focuses on the use of *Channa striata* extract in a gel formulation as a wound therapy with preclinical trials in Wistar rats. Most studies have evaluated *Channa striata* extract in oral preparations, but few in topical preparations, especially gels. Therefore, in this study, we

specifically assessed the effectiveness of snakehead fish extract in gel preparations on wound healing. This study is important to fill this gap and provide scientific evidence on the effectiveness of natural compound-based therapies in the field of orthopedics, while also laying the foundation for future clinical applications.

## METHOD

This study is a laboratory experiment with an *in vivo* approach that aims to determine the effectiveness of snakehead fish (*Channa striata*) extract gel on the wound healing process in Wistar rats. The research design used is a post-test only control group design to study phenomena in cause-and-effect correlations by providing a treatment to research subjects, then observing and studying the effects of the treatment. The study was conducted at the Cendikia Laboratory in collaboration with the University of North Sumatra for one month in June 2025. The study population was male white rats (*Rattus norvegicus*) of the Wistar strain aged 2–3 months with a body weight of 250–300 grams. Samples were selected randomly based on the results of the sample size estimation calculation using the Federer formula, so that a minimum of 9 rats per group were obtained with a total of 27 rats. The inclusion criteria for this study included male Wistar rats weighing 250–300 grams and aged 2–3 months, while the exclusion criteria were rats that were sick, unwilling to eat, or died during the study.

The research variables consisted of the independent variable, namely the administration of snakehead fish extract gel to the wound, and the dependent variable, namely the wound area and histopathology score of wound healing. The wound area was measured using a digital camera and ImageJ software from digital photographs of the wound taken on days 0, 3, 7, and 14, then the percentage of wound closure was calculated. The histopathology score of wound healing was assessed using the HEALS-A scoring system semi-quantitatively with parameters of epithelialization, scarring, angiogenesis, and macrophage or neutrophil infiltration. The score was given a value of 1–4 depending on the histological picture, and one point can be added for each presence of dermal appendages such as hair follicles, glands, or keratin. The score categories include R0 ( $\leq 7$  points, basal stage), R1 (8–10 points, incipient regeneration), R2 (11–15 points, moderate regeneration), R3 (16–20 points, consolidated regeneration), and R4 (21–23 points, total regeneration).

A total of 27 mice were randomly divided into three groups, each consisting of 9 mice. Group 1 as a negative control was not given any topical treatment to assess natural healing. Group 2 as a positive control was given Bioplacenton 0.1 mL once daily on the wound from day 0 to 14, considering the content of placenta extract and neomycin sulfate which are proven to accelerate wound healing. Group 3 was given topical 0.1 mL of snakehead fish extract gel (Vipalbumin gel) once daily from day 0 to 14. Vipalbumin gel is a topical preparation made from *Channa striata* extract produced by PT Continental Cosmetic, Bandung, and is used according to the instructions without modification. This product is stored at a temperature  $<30^{\circ}\text{C}$  and protected from sunlight. Its composition includes *Channa striata* extract, aqua, propylene glycol, hydroxypropyl methylcellulose, polysorbate 80, polyethylene glycol 400, olea europea fruit oil, methylparaben, and sodium chloride.

The test animals were kept in controlled environmental conditions (temperature  $22\text{--}25^{\circ}\text{C}$ , humidity 40–70%, 12-hour light-dark cycle) with access to food and drinking water *ad libitum*, and acclimatized for 7 days before treatment. Excisional wounds were made according to standard protocols using *punch biopsy*. A sterile 8 mm diameter wound was made on the dorsum of mice after intraperitoneal ketamine anesthesia (45 mg/kgBW). Two wounds were made symmetrically to the midline with a minimum distance of 1.5 cm between the wounds (Figure 1) (Muñoz-Torres, Garza-Veloz, Velasco-Elizondo, & Martinez-Fierro, 2025). The wounds were left open for natural healing and then given treatment according to the group. Topical application was carried out once daily for 14 days, and the wounds were documented photographically on days 0, 3, 7, and 14 with a digital

camera, consistent lighting, and distance. The wound area was calculated using ImageJ by calibrating the ruler scale on the photos.

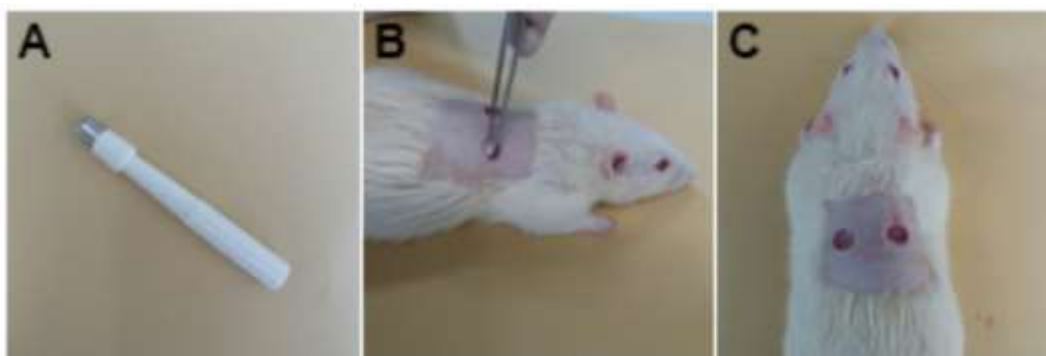


Figure 1. Making an excision wound with a biopsy punch

On days 3, 7, and 14, several mice were euthanized, and the wound tissue and surrounding tissue were removed with a margin of 0.5–1 cm, then fixed in 10% buffered formalin for at least 24 hours. The process of making histopathological slides included dehydration with alcohol, clearing with xylene, paraffin infiltration, paraffin block preparation, 4–5  $\mu\text{m}$  microtome sectioning, deparaffinization, hematoxylin–eosin staining, and mounting. Slides were observed under a light microscope at 400 $\times$  magnification for HEALS-A assessment. Data were analyzed using the Shapiro-Wilk test for normality, ANOVA for differences in mean wound area, Chi-Square for HEALS-A scores, and Bonferroni post hoc if significant. If data were not normal, the Kruskal-Wallis and Fisher Exact tests were used. A p value <0.05 was considered significant. The study has obtained ethical approval from the Ethics Committee of the Faculty of Pharmacy, University of North Sumatra and was conducted in accordance with the 3R principles (Replacement, Reduction, Refinement) without any conflict of interest.

## RESULT

### Characteristics of Research Samples

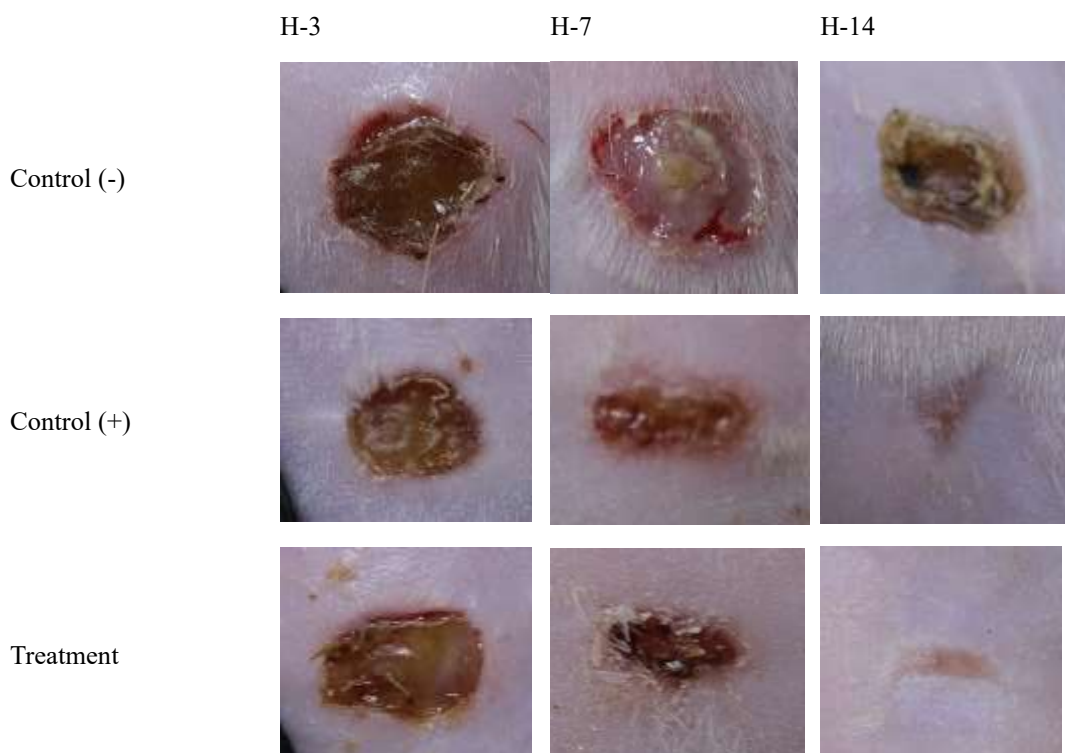


Figure 2. Clinical features of wound development in each research group

A total of 27 mice that met the inclusion and exclusion criteria were randomly divided into three groups, namely a negative control group that was not given any treatment, a positive control group that was given Bioplacenton, and a treatment group that received snakehead fish extract gel (Vipalbumin gel). The three groups of mice were euthanized on days 3, 7, and 14. Direct wound area measurements and tissue sampling were then performed for histological examination. Three groups of nine mice were included in the study, with three mice from each group euthanized on days 3, 7, and 14 after wound creation and treatment. The average wound area and histopathological score were then assessed using the methods described in the previous chapter. The following is a clinical description of the development of wounds from each research group, which is shown in Figure 2.

The results of the normality test with Shapiro-Wilk showed that the data distribution was normally distributed with a significance value  $> 0.05$ , where on day 3 the p-value for the control (-) was 0.055, the control (+) was 0.934, and the treatment was 0.804. Likewise on days 7 and 14, the data distribution was normally distributed with a significance value  $> 0.05$ .

Table 1.

Results of the Shapiro-Wilk normality test for wound area

Group	Day 3 (SW/Sig)	Day 7 (SW/Sig)	Day 14 (SW/Sig)
Control (-)	0.797 / .055	0.867 / .215	0.989 / .987
Control (+)	0.977 / .934	0.895 / .343	0.878 / .259
Treatment	0.958 / .804	0.867 / .214	0.958 / .807

Notes: SW: Shapiro-Wilk

The histopathological description and frequency distribution of each histopathological wound healing score parameter from each group are shown in Figures 3, 4 and Table 2 below.

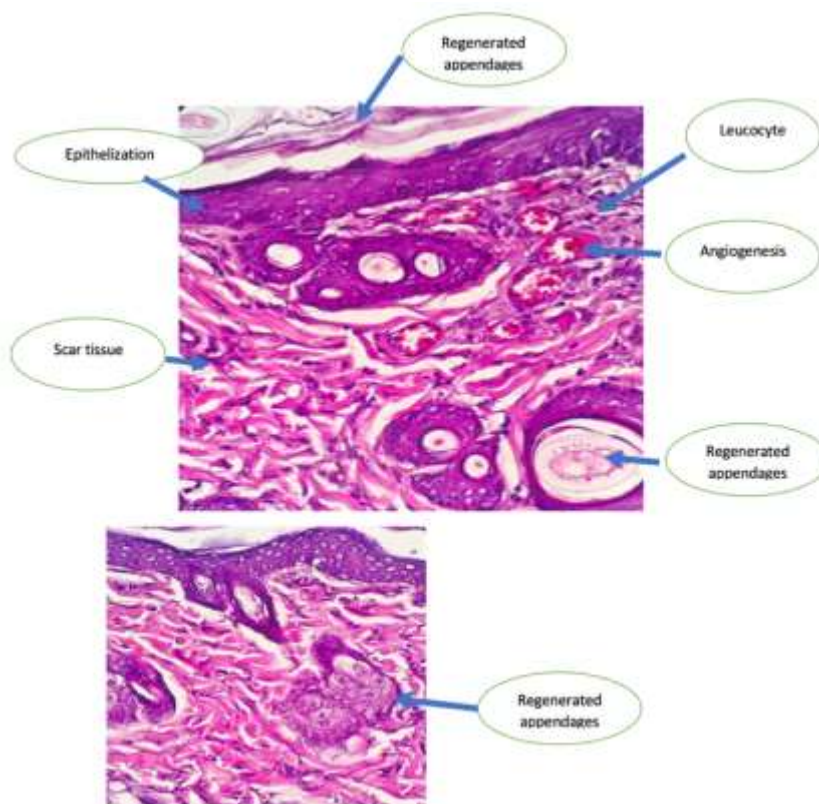


Figure 3. Histopathological examination of wound healing

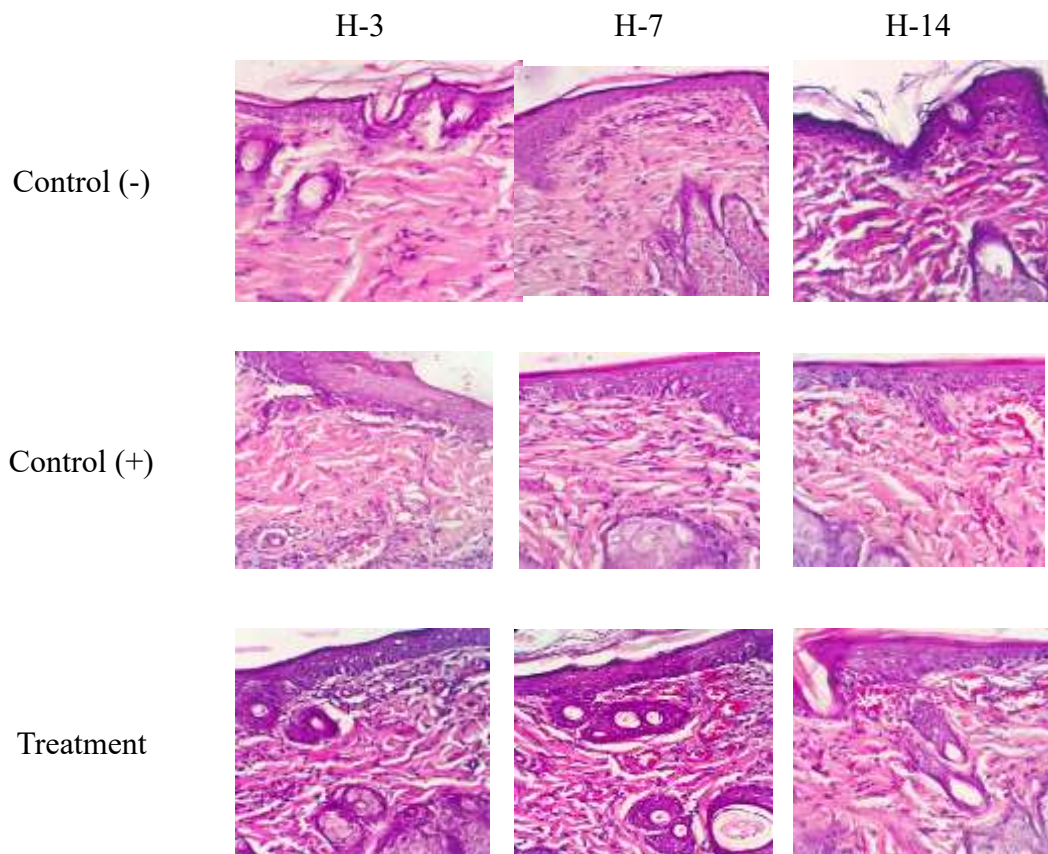


Figure 4. Histopathological description of wound healing from each research group  
Table 2.

Frequency distribution of each parameter of the HEALS-A histopathology score

Parameter	Control (-)			Control (+)			Treatment		
	Day 3	Day 7	Day 14	Day 3	Day 7	Day 14	Day 3	Day 7	Day 14
Epithelialization	1.7 ± 0.6	3 ± 0	2.3 ± 0.6	2.7 ± 0.6	2.7 ± 1.2	3.7 ± 0.6	3.3 ± 0.6	3 ± 0	3.3 ± 0.5
Angiogenesis	1.3 ± 0.6	1 ± 0	2.3 ± 0.6	2.3 ± 0.6	2 ± 0	4 ± 0	3.7 ± 0.6	3.3 ± 0.6	4 ± 0
Neutrophils	1.3 ± 0.6	1.7 ± 0.6	3 ± 0	2.3 ± 0.6	4 ± 0	4 ± 0	2 ± 0	3.7 ± 0.6	4 ± 0
Macrophages	1 ± 0	1.7 ± 0.6	3 ± 0	2.3 ± 0.6	2.3 ± 0.6	4 ± 0	2 ± 0	3.3 ± 1.5	4 ± 0
Scar tissue	1.3 ± 0.6	2.7 ± 0.6	2.7 ± 1.2	1.3 ± 0.6	2.3 ± 0.6	3.3 ± 0.6	2.7 ± 0.6	2.7 ± 0.6	4 ± 0
Hair follicles	1 ± 0	0.7 ± 0.6	0.3 ± 0.6	1 ± 0	0.7 ± 0.6	1 ± 0	0.3 ± 0.6	1 ± 0	1 ± 0
Gland	0.3 ± 0.6	1 ± 0	1 ± 0	0.7 ± 0.6	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
Keratin	1 ± 0	0.7 ± 0.6	0.7 ± 0.6	0.7 ± 0.6	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0

**Differences in clinical parameters of wound healing by measuring the average wound area in groups of Wistar rats treated with snakehead fish (*Channa Striata*) extract gel compared to the control group.**

An assessment of differences in clinical parameters of wound healing was carried out by measuring the average wound area in the group of Wistar rats treated with snakehead fish (*Channa Striata*) extract gel compared to the control group. In table 3, it can be seen that the average wound area on day 3 (D-3) for the control group (-) was 74.2 ± 31.9 mm<sup>2</sup> (95% CI: 40.7–107.8), the control (+) was 53.1 ± 14.0 mm<sup>2</sup> (38.4–67.7), and the treatment group was 38.9 ± 19.5 mm<sup>2</sup> (18.4–59.4), with a p-value in the ANOVA test of 0.054, approaching the significance threshold. On the 7th day (D-7),

the average wound area in the control group (-) was  $67.6 \pm 49.2 \text{ mm}^2$  (95% CI: 15.9–119.2), the control (+) was  $9.7 \pm 4.8 \text{ mm}^2$  (4.7–14.7), and the treatment group was  $27.4 \pm 17.9 \text{ mm}^2$  (8.7–46.2), which showed a significant difference in the ANOVA test with a p-value of 0.014 ( $p < 0.05$ ). Likewise on the 14th day (D-14), where the average wound area in the control group (-) was recorded at  $54.2 \pm 32.5 \text{ mm}^2$  (20.1–88.3), the control (+) was  $6.7 \pm 2.5 \text{ mm}^2$  (4.1–9.4), and the treatment group was  $7.1 \pm 2.8 \text{ mm}^2$  (4.2–10.0), with a p-value of  $<0.001$ , indicating a significant difference. These values illustrate a downward trend in the average wound area. Overall, the results of the ANOVA test support the hypothesis of differences in effectiveness between the three groups, especially on the 7th and 14th days.

Table 3.  
ANOVA test of the mean wound area between groups

Variables	Group	Mean $\pm$ SD	p-value
Day 3	Control (-)	74.2 $\pm$ 31.9 (15.35%)	.054
	Control (+)	53.1 $\pm$ 13.9 (39.49%)	
	Treatment	38.9 $\pm$ 19.5 (55.64%)	
Day 7	Control (-)	67.6 $\pm$ 49.2 (22.93%)	.014
	Control (+)	9.7 $\pm$ 4.8 (88.96%)	
	Treatment	27.4 $\pm$ 17.9 (68.7%)	
Day 14	Control (-)	54.2 $\pm$ 32.5 (38.21%)	< .001
	Control (+)	6.7 $\pm$ 2.5 (92.3%)	
	Treatment	7.1 $\pm$ 2.8 (91.87%)	

The results obtained for significance from the previous difference calculations were followed up with a Post Hoc test using Bonferroni to assess the comparison of each variable (Table 4.4). Based on Table 4, on the 7th day only the comparison between the control (-) and control (+) showed a significant difference ( $p = 0.014$ ), while the treatment group did not show a significant difference. However, on the 14th day, a significant difference was seen between the control (-) and control (+) groups ( $p = 0.002$ ) and with the treatment group ( $p = 0.002$ ), indicating that both intervention and treatment were effective in accelerating wound healing. There was no significant difference between the control (+) and treatment groups, indicating that both had equivalent effectiveness in reducing wound area after 14 days.

Table 4.  
Bonferroni Posthoc Test on wound area between groups.

Day to	Group 1	Group 2	p-value
H-7	Control -	Control +	.014
	Control -	Treatment	.111
	Control +	Treatment	.981
H-14	Control -	Control +	.002
	Control -	Treatment	.002
	Control +	Treatment	1,000

**Differences in histopathological parameters of wound healing through the HEALS A score in the group of Wistar rats treated with snakehead fish (*Channa striata*) extract gel compared to the control group.**

An assessment of the differences in histopathological parameters of wound healing was carried out using the HEALS-A score in groups of Wistar rats given Treatment of snakehead fish (*Channa striata*) extract gel was compared with the control group. The HEALS-A score showed differences in histological parameters of wound healing between groups (Table 5). On day 3 in the control group, all samples showed a HEALS-A score of R1, in the control+ group, all samples showed a HEALS-A score of R2, and in the treatment group, 2 samples showed a HEALS-A score of R2 and 1 sample R3. Statistical tests were performed and significant differences were found between the treatment and the histological parameters of HEALS-A ( $p < 0.001$ ). On day 7 in the control group, all samples showed a HEALS-A score of R2, in the control+ group, 2 samples showed a HEALS-A score of R2 and 1 sample R3, and in the treatment group, all samples showed a HEALS-A score of R3. Statistical tests were performed and significant differences were found between the treatment

and the histological parameters of HEALS-A ( $p = 0.001$ ). On the 14th day in the control group, all samples showed a HEALS-A score of R3, in the control group+ all samples showed a HEALS-A score of R4 and in the treatment group all samples showed a HEALS-A score of R4. Statistical tests were carried out and a significant difference was found between the administration of treatment and the histological parameters of HEALS-A ( $p = 0.001$ ).

Table 5.

Mean total HEALS-A score on histopathological examination of wound healing between groups.

Variables	Group	HEALS-A Score					p-value
		R0	R1	R2	R3	R4	
Day 3	Control-	0	3	0	0	0	<0.001
	Control+	0	0	3	0	0	
	Treatment	0	0	2	1	0	
Day 7	Control-	0	0	3	0	0	0.001
	Control+	0	0	1	2	0	
	Treatment	0	0	0	3	0	
Day 14	Control-	0	0	0	3	0	0.001
	Control+	0	0	0	0	3	
	Treatment	0	0	0	0	3	

## DISCUSSION

### Differences in mean wound area between study groups

Clinical evaluation of wound healing based on mean wound area showed differences in dynamics between groups over time. On day 3, the Vipalalbumin gel treatment group had the smallest mean wound area ( $38.9 \pm 19.5 \text{ mm}^2$ ) compared to the positive control ( $53.1 \pm 14.0 \text{ mm}^2$ ) and negative control ( $74.2 \pm 31.9 \text{ mm}^2$ ). Although not yet statistically significant, this trend indicates an initial therapeutic effect, possibly hampered by the small sample size. Clinically, these results imply that the bioactive components of *Channa striata* begin to work from the beginning of application, modulating the wound environment and accelerating the healing cascade compared to the natural process.

On day 7, the mean wound area showed a significant difference, with the positive control (Bioplacenton) experiencing the fastest reduction ( $9.7 \pm 4.8 \text{ mm}^2$ ), surpassing the Vipalalbumin gel group ( $27.4 \pm 17.9 \text{ mm}^2$ ). Post-hoc testing confirmed the superiority of Bioplacenton over the negative control, while Vipalalbumin did not differ significantly. This difference is influenced by the mechanism of action of both agents; Bioplacenton is rich in growth factors such as EGF and FGF which directly stimulate keratinocyte migration and proliferation, accelerating epithelial closure (Protzman et al., 2023). In contrast, Vipalalbumin only provides nutrient precursors (albumin, amino acids, minerals) that must be processed by host cells for growth factor and ECM synthesis, so its effect is slower at this stage (Oslan et al., 2022).

On day 14, the Vipalalbumin gel group ( $7.1 \pm 2.8 \text{ mm}^2$ ) achieved wound closure equivalent to the positive control ( $6.7 \pm 2.5 \text{ mm}^2$ ) and both were significantly better than the negative control. These findings indicate that continuous nutritional support from Vipalalbumin gel is capable of producing wound healing as effective as direct stimulation from Bioplacenton. Snakehead fish extract (albumin) contains amino acids with a more complete structure, which is essential for the body compared to other protein sources. Therefore, snakehead fish extract (albumin) is an alternative to help increase albumin levels and aid in post-operative wound healing. 100% snakehead fish extract has a higher impact because it contains more active substances that can improve the wound healing process. Snakehead fish extract is rich in essential minerals for the body such as zinc (Zn), copper (Cu), iron (Fe), and polyunsaturated fatty acids. The copper mineral contained in it, increases and produces fibroblast growth factor (FGF) which leads to an increase in fibroblast cells. Cu and Zn play a role in binding and optimizing the function of the superoxide dismutase (SOD) enzyme to reduce inflammation. Iron helps deliver oxygen and collagen synthesis during the wound healing

process. The extract gel also contains unsaturated fatty acids that play an important role in the regulation and synthesis of prostaglandins, chemical mediators that appear during inflammation activating macrophages. Therefore, the higher the level of prostaglandins, the faster the process of phagocytosis and clearance of debris tissue, thereby accelerating the inflammation process. Kandungan ekstrak ikan gabus meningkatkan aktivitas antioksidan albumin yang mengatur jumlah makrofag. Furthermore, minerals such as Cu, Fe, Mg and unsaturated fatty acids which play a role in reducing ROS and accelerating the inflammatory process are added to accelerate growth factor formation and the healing process. The strategy of providing albumin, amino acids, and minerals has been shown to be effective in promoting optimal wound closure within a clinically relevant timeframe (Tarannum, Islam, Shariar, & Islam, 2025).

### **Differences in histopathology wound healing scores (HEALS-A) between study groups**

On day 3, the HEALS-A score showed that the negative control was entirely R1, the positive control was R2, and the treatment group had 2 R2 samples and 1 R3 sample. This indicates that since the inflammatory phase, the treatment and positive control were able to modulate the inflammatory response more effectively, indicated by more controlled neutrophil and macrophage infiltration and faster resolution compared to the negative control. This effect is related to the bioactive content of *Channa striata*, especially omega-3 which is a precursor of specialized pro-resolving mediators (SPMs) such as resolvin and maresin which actively regulate inflammation resolution. Wound healing is very likely to require protein, among other essential substances, as a basis for the formation of collagen tissue. Administration of snakehead fish albumin functions as a binding and transporting agent, regulating osmotic pressure, inhibiting platelet formation and anti-thrombosis. Snakehead fish is one type of fish that is widely used for the wound healing process, especially post-operative wounds, because the main content in snakehead fish is protein or albumin which is quite high and also albumin is the most abundant protein in plasma, around 60% of total plasma protein with a normal value of 3.3–5.5 g/dl albumin is also found in the extracellular space 40% is found in plasma and 60% extracellular. Meanwhile, one of the factors in the process of accelerating wound healing is the need for high protein found in snakehead fish (Mateu-Arrom, Mora, & Garrote, 2025; Rita El Jbeily et al., 2024; Setyowiranti & Darmaputra, 2023).

The increase in the number of macrophages on day 1 is due to the filtration of inflammatory cells into the wound area, macrophages become active and their number doubles when inflammation occurs. After 2-3 days of wound formation, granulation tissue forms. Histologically, the formation of granulation tissue is characterized by the proliferation of fibroblasts and new, smooth, thin-walled capillaries. During wound healing, fibroblasts actively move from the surrounding tissue into the wound area, then develop or proliferate and release several substances, namely collagen, elastin, fibronectin, hyaluronic acid, fibronectin, and proteoglycans, which play a role in the reconstruction of new tissue. Zinc plays a role in accelerating the wound healing process by reducing inflammation and stimulating re-epithelialization. Copper and Fe contained in snakehead fish extract are also compounds that help collagen synthesis and proliferation. If zinc deficiency occurs along with copper, it results in decreased phagocytic ability in the immune system, impaired microbial destruction, and disruption of the wound healing process and the microbial activity of phagocytic cells. Meanwhile, Fe deficiency can cause anemia which results in reduced blood and oxygen supply to the wound area and a decrease in the ability of inflammatory cells to phagocytose bacteria so that the wound healing process is disrupted. This mechanism is thought to trigger the transition of M1 to M2 macrophages which play a pro-reparative role (Apriasari, Puspitasari, & Utami, 2022; Ramadhanti et al., 2021). The rapid decrease in inflammatory cells in the treatment group reflects active modulation towards a microenvironment that supports a faster and optimal proliferation phase.

On day 7, all negative control samples were at R2, positive controls consisted of 2 R2 samples and 1 R3 sample, while all treatment groups had reached R3. Although the wound area of the treatment

group was not clinically significantly different from the positive control, its histopathological progress was faster, marked by higher angiogenesis and early epithelialization, characteristic of the proliferation phase (days 3–21). The angiogenesis score in the treatment group was consistently superior (D-3:  $3.7\pm 0.6$ ; D-7:  $3.3\pm 0.6$ ) compared to the positive and negative controls. This pro-angiogenic effect is triggered by the bioactive content of *Channa striata* which increases VEGF expression, provides Zn as a cofactor for endothelial proliferation, and arginine as a precursor of NO to support neovascularization (Apriasari et al., 2022; Arribas Lopez, Zand, Ojo, & Kochhar, 2025; Yahya et al., 2025). The combination of oxygen supply, nutrients, albumin, and essential amino acids creates ideal conditions for keratinocyte migration and rapid and high-quality epithelial closure (Lee et al., 2022; Yuliana et al., 2022).

On day 14, all negative control samples were at R3, while the positive and treatment controls achieved the highest HEALS-A score of R4, consistent with equal wound area on the same day. This indicates that both interventions successfully promoted healing to the remodeling phase with good tissue quality. The scar tissue score in the treatment group was higher ( $4\pm 0$ ) than the positive ( $3.3\pm 0.6$ ) and negative ( $2.7\pm 1.2$ ) controls, indicating more mature and organized collagen deposition. Interestingly, from day 3, ECM deposition in the treatment group was already higher, indicating an efficient inflammatory-proliferative transition (Moretti, Stalfort, Barker, & Abebayehu, 2022). Rapid resolution of inflammation allows fibroblasts to migrate earlier and, aided by the glycine and proline content of *Channa striata* extract, accelerates collagen synthesis (Quan, 2026; Singh, Rai, & Agrawal, 2023; Zang et al., 2025). This combination explains the acceleration of ECM deposition and remodeling that potentially results in scar tissue with more mature collagen and better tensile strength (Lee et al., 2022; Yuliana et al., 2022).

## CONCLUSION

A significant difference was seen in the average wound area between the control and treatment groups, especially on days 7 and 14, indicating that the administration of *Channa striata* extract gel was able to accelerate the wound healing process clinically. On day 3, the difference was not yet clearly visible, but the trend of reducing wound area in the treatment group appeared more consistent and stable compared to the two control groups. In addition, histopathological assessment also showed significant differences between groups throughout the observation period, indicating that *Channa striata* extract gel played a role in improving the quality of wound healing microscopically.

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