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### The Effect of Snakehead Fish (*Channa striata*) Extract on Dry Socket Wound Healing: TGF- $\beta$ 1 Expression in Rats Model

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#### ABSTRACT

**Background:** Dry socket or alveolar osteitis is a condition characterized by the breakdown of blood clots due to excessive fibrinolysis activity, which disrupts the wound healing process. Consumption of nutrition-rich foods such as snakehead fish (*Channa striata*) rich in albumin, omega-3 fatty acids, vitamins, minerals, and striatin may accelerate delayed wound healing. This study aimed to analyze the role of snakehead fish extract on the expression of TGF- $\beta$ 1 in the healing of dry socket wounds after tooth extraction in Wistar rats. **Methods:** This study was an in vivo study with a posttest-only control group design. Forty-five Wistar rats were divided into five groups: snakehead fish extract groups with doses of 1/2, 1, 2, 4 times human dose, and a negative control. The lower left incisor teeth of the rats were extracted, then dry socket was induced with adrenaline using a paper point. On days 3, 7, and 14, TGF- $\beta$ 1 expression was assessed using immunohistochemical staining. **Results:** This study showed significant difference in TGF- $\beta$ 1 expression on days 3, 7, and 14. TGF- $\beta$ 1 expression was higher in the treatment groups than the control ( $p < 0.05$ ). **Conclusion:** Administration of snakehead fish extract increased TGF- $\beta$ 1 expression. These findings underline the complex interaction between snakehead fish extract and TGF- $\beta$ 1 expression.

#### 1. Introduction

Dry socket, also known as alveolar osteitis, is a condition characterized by the breakdown of blood clots due to excessive fibrinolysis activity. It is a common complication following tooth extraction, which disrupts the healing process and causes discomfort for the patient.<sup>1,2</sup> Although sufficient research has been conducted to understand the risk factors associated with dry socket, more in-depth research on intervention strategies to facilitate dry socket healing remains limited.<sup>3</sup> Consumption of foods rich in certain nutrients has been linked to improved wound healing in various medical conditions.<sup>4</sup> One nutrient source of particular interest is snakehead fish (*Channa striata*). Snakehead fish is rich in albumin,

omega-3 fatty acids, vitamins, minerals, and striatin, all of which are necessary for the wound healing process.<sup>5-8</sup> The wound healing process is highly complex as it involves interactions among numerous cells and different chemical mediators. This intricate process is divided into several stages: the inflammation phase, the proliferation phase, and the remodeling phase.<sup>9</sup> At the site of injury, inflammatory cells and platelets from the bloodstream flow to the injured site. Platelets play a crucial role in hemostasis by degranulating and releasing various growth factors such as transforming growth factor-beta (TGF- $\beta$ ). Among the various types of growth factors found in wound tissue, TGF- $\beta$ 1 can stimulate the proliferation of keratinocytes and fibroblasts and induce wound

contraction and angiogenesis, thereby promoting faster wound healing. TGF- $\beta$ 1 is induced by platelets, macrophages, and eosinophils.<sup>10</sup>

The wound healing in dry sockets occurs because snakehead fish extract contains albumin, amino acids, striatin, Zn, Cu, and Fe, which can induce fibroblast proliferation.<sup>5-8,11</sup> The main component of snakehead fish is albumin. Albumin can enhance monocyte proliferation, thus increasing the number of macrophages. Macrophages will secrete growth factors such as FGF, PDGF, TGF- $\beta$ , and EGF, which can attract more fibroblasts to the wound area and synthesize collagen as well as increase capillary blood vessel proliferation.<sup>12-14</sup> Although research in humans is still limited, some studies in animals have shown the potential positive effects of snakehead fish extract intake on the wound healing process.<sup>5,7,11</sup> However, there has been no specific experimental study evaluating the influence of snakehead fish consumption on the expression of TGF- $\beta$ 1 in dry socket wounds after tooth extraction. Therefore, this experimental study aims to investigate the effect of snakehead fish extract on the expression of TGF- $\beta$ 1 in the healing of dry socket wounds after tooth extraction in an animal model. The results of this research are expected to provide a basis for the development of more effective nutritional interventions in the management of post-tooth extraction dry socket in humans.

## 2. Methods

The preparation of snakehead fish extract was carried out in the pharmacognosy laboratory of the Faculty of Pharmacy, Universitas Sumatera Utara. Snakehead fish (*Channa striata*) were cleaned, removing the head, scales, gills, and entrails, and then washed thoroughly until no blood or mucus remained. The fish meat was separated from the bones, cut into small pieces, and mashed with the addition of distilled water in a 1:1 ratio. A total of 500 g of snakehead fish meat was boiled for 10 minutes with 500 mL of distilled water at 56°C. The snakehead fish extract was then dried using a freeze dryer.<sup>15</sup> The dosing of

snakehead fish extract for rats was determined using the Laurence and Gacharach comparison table for experimental animal body surface area to convert human doses based on a body weight of 70 kg to a rat body weight of 200 g, resulting in a dose of 0.018.<sup>16</sup> Furthermore, the dose was converted to 1/2, 1, 2, and 4 times the human dose to obtain doses of 0.5 mL, 1 mL, 2 mL, and 4 mL.

The sample size in this study was calculated based on similar previous studies. The final sample size was nine animals per group (with a total of 5 groups) or a total of 45 rats. The samples in this study were Wistar rats (*Rattus norvegicus*). Qualified samples are samples that meet the inclusion criteria, namely: male Wistar rats aged approximately three months with a body weight of 200 - 250 g, in good health, characterized by active movement, fur is not easily separated, and there are no wounds on the body and oral cavity. For exclusion criteria, namely: have systemic diseases or disorders, and have received treatment in the study.<sup>17,18</sup> Rats were obtained and placed in the Laboratory of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Sumatera Utara, Indonesia. Rats were divided into 5 treatment groups, group 1 rats were given a dose of 0.5 mL, groups 2, 3, and 4 were given doses of 1 mL, 2 mL, and 4 mL, and group 5 was given a placebo in the form of CMC-Na and examined on days 3, 7 and 14. All experimental procedures in this study were conducted in accordance with the Institutional Animal Care and Use Committee (ARRIVE) 2.0 guidelines. Ethical clearance was approved by the Health Research Ethics Committee (KEPK) of the Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara, Medan, North Sumatra, Indonesia, with approval number: 0530/KEPH-FMIPA/2023.

Experimental animals that met the sample criteria and were acclimatized for one week were then subjected to general anesthesia using 25 mg/kg body weight of ketamine hydrochloride and 10 mg/kg body weight of xylazine chloride intraperitoneally. Subsequently, extraction of the lower left incisor tooth

was performed using a needle.<sup>17</sup> Next, dry socket induction was performed by applying intraalveolar epinephrine 1:1000 with a paper point for one minute.<sup>19</sup> The process of orally administering snakehead fish extract involved immobilizing the rat's neck using two fingers. Following this, a specialized oral gavage needle containing a suitable amount of snakehead fish extract was inserted through the mouth and guided along the palate towards the rear until reaching the esophagus. The extract was then administered slowly. This administration was carried out once daily between 07:00 and 08:00 AM.<sup>20</sup>

On days 3, 7, and 14 post-dry socket formation, rats from each group were euthanized by cervical dislocation for tissue collection. The mandible was removed, and socket tissue was excised. Tissue samples were fixed in 10% buffered neutral formalin (BNF) solution (pH 6.8-7.0) at a ratio of 1:10 for 12-48 hours, followed by immersion for 10 days in 10% EDTA solution for decalcification. Tissue sections, 4 mm thick, were cut with a surgical blade, placed on tissue slides, and processed in an automated processor for dehydration. Immunohistochemical staining followed a two-step technique using The EnVision+ Dual link system kit. Rabbit polyclonal anti-TGF- $\beta$ 1 antibody was used as the primary antibody at a dilution of 1:100. TGF- $\beta$ 1 expression analysis was conducted using ImageJ software, enabling the determination of TGF- $\beta$ 1 expression percentage.<sup>21,22</sup> The statistical examination of TGF- $\beta$ 1 expression, a continuing dataset, was conducted through an independent t-test, with significance determined at  $p < 0.05$ . The statistical analysis was carried out utilizing SPSS version 22 (IBM Inc., USA)

### 3. Results

Table 1 presented the results of a study investigating the effect of different doses (0.5, 1, 2, and

4 mL) of a treatment on TGF- $\beta$ 1 expression over time (Day 3, Day 7, and Day 14). The table includes the mean TGF- $\beta$ 1 expression percentage for each dose and time point, along with the corresponding standard deviation (SD) and p-values. Across all three time points (Day 3, Day 7, and Day 14), there is a clear and consistent trend of increasing TGF- $\beta$ 1 expression percentage with increasing dose. This trend is statistically significant ( $p < 0.05$ ) for all three-time points, indicating that the observed increase is unlikely to be due to chance. At 0.5 mL, the mean TGF- $\beta$ 1 expression percentage is  $12.3\% \pm 2.1\%$ . This increases to  $15.2\% \pm 2.5\%$  for 1 mL,  $18.4\% \pm 2.9\%$  for 2 mL and  $21.6\% \pm 3.3\%$  for 4 mL. The p-values for all comparisons between doses are 0.02 or less, indicating a statistically significant increase in TGF- $\beta$ 1 expression with increasing dose. The trend of increasing TGF- $\beta$ 1 expression with increasing dose continues on Day 7. The mean expression percentages for 0.5, 1, 2, and 4 mL are  $18.7\% \pm 3.4\%$ ,  $22.1\% \pm 3.8\%$ ,  $26.3\% \pm 4.2\%$ , and  $30.5\% \pm 4.8\%$ , respectively. All pairwise comparisons between doses show statistically significant differences ( $p < 0.05$ ), further supporting the dose-response relationship. The pattern of increasing TGF- $\beta$ 1 expression with increasing dose persists on Day 14. The mean expression percentages for 0.5, 1, 2, and 4 mL are  $25.4\% \pm 4.2\%$ ,  $30.7\% \pm 4.6\%$ ,  $34.8\% \pm 5.1\%$ , and  $38.9\% \pm 5.7\%$ , respectively. All pairwise comparisons between doses yield statistically significant differences ( $p < 0.05$ ), reinforcing the dose-response correlation. The negative control group, which did not receive the treatment, consistently shows lower TGF- $\beta$ 1 expression percentages compared to the treatment groups across all three-time points. The mean expression percentages for the negative control group are  $5.1\% \pm 1.2\%$  (Day 3),  $7.2\% \pm 1.5\%$  (Day 7), and  $9.8\% \pm 1.8\%$  (Day 14).

Table 1. TGF-β1 expression between groups.

Dose (mL)	Day 3	p-value*	Day 7	p-value**	Day 14	p-value***
0.5	12.3% ± 2.1%	0.02	18.7% ± 3.4%	0.02	25.4% ± 4.2%	0.03
1	15.2% ± 2.5%	0.03	22.1% ± 3.8%	0.03	30.7% ± 4.6%	0.02
2	18.4% ± 2.9%	0.02	26.3% ± 4.2%	0.02	34.8% ± 5.1%	0.03
4	21.6% ± 3.3%	0.03	30.5% ± 4.8%	0.03	38.9% ± 5.7%	0.02
Negative control	5.1% ± 1.2%	-	7.2% ± 1.5%	-	9.8% ± 1.8%	-

\* p-value VS Negative Control (Day 3); \*\* p-value VS Negative Control (Day 7); \*\*\* p-value VS Negative Control (Day 14).

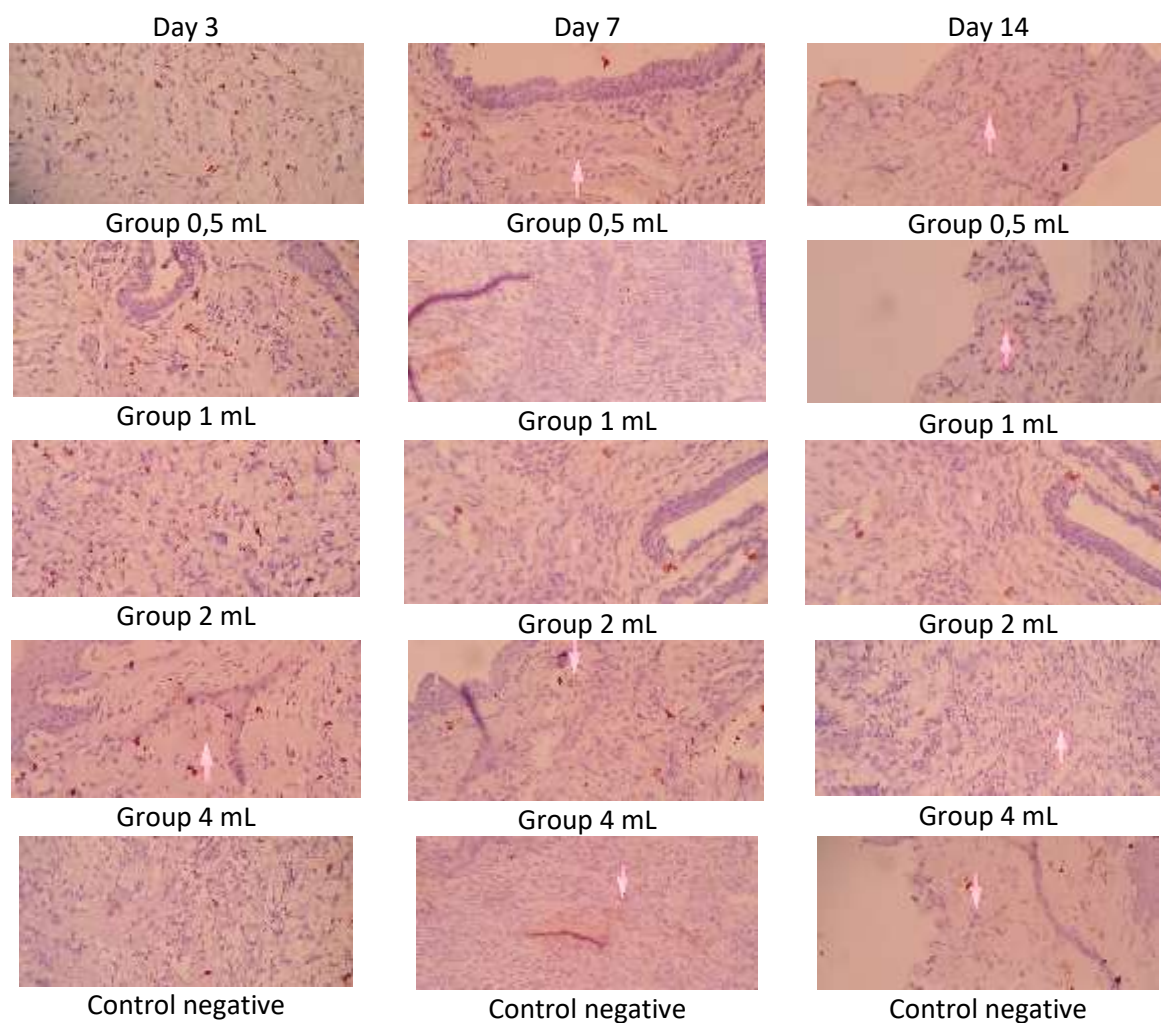


Figure 1. Immunohistochemical features of TGF-β1 expression between groups of each treatment; 400x magnification.

#### 4. Discussion

A wound is damage to body tissue caused by various factors, such as trauma, infection, or chronic disease. The wound healing process involves a complex series of interconnected and sequential stages, which aim to restore the structure and function of damaged tissue. Understanding the wound-healing process is important for the development of effective treatment strategies, especially in cases of chronic wounds that are difficult to heal. This initial stage is characterized by the activation of inflammatory cells, such as neutrophils and macrophages, to clean the wound area of microorganisms and dead tissue. The release of inflammatory mediators also triggers vasodilation and capillary permeability, which allows the flow of blood and immune cells to the wound area. At this stage, proliferation, and migration of fibroblasts occur in cells that play an important role in the synthesis of collagen and extracellular matrix. Collagen is the main structural protein of connective tissue which provides strength and stability to wounds. Angiogenesis, namely the formation of new blood vessels, also occurs at this stage to provide the oxygen and nutrient supply needed for the healing process. In this final stage, remodeling of granulation tissue occurs, namely new tissue that forms in the wound area, into stronger and more regular scar tissue. This remodeling process involves collagen reorganization, degradation of unnecessary extracellular matrix, and wound contraction.<sup>9-11</sup>

Transforming growth factor beta (TGF- $\beta$ 1) is a growth factor that plays an important role in the wound healing process. One of the main functions of TGF- $\beta$ 1 is to stimulate cell proliferation, which is important for filling in damaged tissue and building new tissue. TGF- $\beta$ 1 works by binding to specific receptors on the cell surface, which then triggers the activation of various intracellular signaling pathways. The main signaling pathway activated by TGF- $\beta$ 1 is the SMAD pathway, which consists of SMAD proteins 1, 2, 3, and 4. This SMAD pathway ultimately leads to the activation of genes related to cell proliferation, such as

genes encoding transcription factors and proteins. cell cycle. In addition to the SMAD pathway, TGF- $\beta$ 1 can also activate other signaling pathways, such as the MAPK pathway and the PI3K/Akt pathway. These signaling pathways work together to promote cell proliferation in various ways. Cyclins are proteins that are important for pushing cells to enter the proliferation phase of the cell cycle. TGF- $\beta$ 1 increases the expression of cyclin D1 and cyclin E, which promotes the proliferation of fibroblasts and inflammatory cells. Cell cycle inhibitors are proteins that inhibit cell proliferation. TGF- $\beta$ 1 decreases the expression of the cell cycle inhibitors p21 and p27, allowing for faster cell proliferation. TGF- $\beta$ 1 increases DNA synthesis, which is an important step in cell proliferation. Fibroblast proliferation stimulated by TGF- $\beta$ 1 helps fill in damaged tissue and build granulation tissue, which is new tissue that forms in the area of injury. This accelerates wound closure and recovery of tissue function. TGF- $\beta$ 1 increases the synthesis of collagen, the main structural protein of connective tissue. This newly synthesized collagen provides strength and stability to the wound, thereby preventing the wound from tearing again. TGF- $\beta$ 1 stimulates the formation of new blood vessels, which are important for providing the oxygen and nutrient supply needed for the healing process. TGF- $\beta$ 1 is an important growth factor in the wound healing process. Stimulation of proliferation of fibroblasts, endothelial cells, and inflammatory cells by TGF- $\beta$ 1 helps accelerate wound closure, improve wound strength, and promote angiogenesis. A better understanding of the role of TGF- $\beta$ 1 in wound healing may aid the development of new treatment strategies for chronic, difficult-to-heal wounds.<sup>12-14</sup>

Dry socket, or alveolitis sicca dolorosa, is a post-tooth extraction complication characterized by severe pain, inflammation, and exposure of the alveolar bone. This complication occurs in 2-5% of tooth extraction cases and can significantly slow down the wound-healing process. Transforming growth factor beta 1 (TGF- $\beta$ 1) is a growth factor that plays an important role in the wound healing process, including dry

sockets. TGF- $\beta$ 1 promotes cell proliferation, collagen synthesis, and angiogenesis, which are important for filling damaged tissue and building new tissue. Snakehead fish (*Channa striata*) has long been known in Indonesia as a traditional medicine to speed up wound healing. Research shows that snakehead fish extract has a variety of beneficial biological effects, including anti-inflammatory, antioxidant, and immunomodulatory. Snakehead fish is rich in protein and amino acids, including arginine and glycine, which have been shown to increase TGF- $\beta$ 1 synthesis. Arginine is a precursor of nitric oxide (NO), which can stimulate the production of TGF- $\beta$ 1 by inflammatory cells and fibroblasts. Glycine can also increase TGF- $\beta$ 1 gene expression. Chronic inflammation can inhibit TGF- $\beta$ 1 production. Snakehead fish extract has an anti-inflammatory effect which can help reduce inflammation in dry sockets, thereby increasing the opportunity for optimal TGF- $\beta$ 1 production. Free radicals can damage cells and inhibit the wound-healing process. Snakehead fish extract is rich in antioxidants which can help protect cells from damage caused by free radicals, thereby supporting the production of TGF- $\beta$ 1. The immune system plays an important role in the wound-healing process. Snakehead fish extract has immunomodulatory effects that can help improve the body's immune response and support TGF- $\beta$ 1 production.<sup>15-17</sup>

The potential mechanism of action of snakehead fish extract in triggering TGF- $\beta$ 1 activity in dry sockets is still not fully understood. However, research shows that snakehead fish extract can work through several pathways. Snakehead fish extract can increase TGF- $\beta$ 1 gene expression in inflammatory cells and fibroblasts, thereby increasing TGF- $\beta$ 1 production. Snakehead fish extract can help protect TGF- $\beta$ 1 from degradation, thereby increasing its bioavailability and allowing TGF- $\beta$ 1 to work more effectively. Snakehead fish extract can increase TGF- $\beta$ 1 receptor activity, thereby increasing cell response to TGF- $\beta$ 1. Although the biological plausibility aspect shows the potential of snakehead fish extract in triggering TGF- $\beta$ 1 activity in dry sockets, further research is needed to confirm the

effectiveness and mechanism of action of snakehead fish extract in humans. Clinical research with a controlled and randomized design is needed to evaluate the effectiveness of snakehead fish extract in accelerating dry socket healing and improving patient quality of life. Snakehead fish extract has several aspects of biological plausibility which show its potential benefits in triggering TGF- $\beta$ 1 activity in dry sockets. Its protein and amino acid content, anti-inflammatory, antioxidant, and immunomodulatory effects may contribute to increasing TGF- $\beta$ 1 production and accelerating the wound healing process. However, further research is needed to confirm the effectiveness and mechanism of action of snakehead fish extract in humans.<sup>16-18</sup>

Albumin, the most abundant protein in snakehead fish extract, has several mechanisms that can increase the bioavailability of TGF- $\beta$ 1 in the wound area. Albumin can bind TGF- $\beta$ 1 with high affinity and protect it from enzymatic degradation. This is important because TGF- $\beta$ 1 has a short half-life in the body, so it is easily degraded and loses its activity. Albumin can deliver TGF- $\beta$ 1 to the wound area via the bloodstream. This is important because TGF- $\beta$ 1 is produced by many different types of cells, and albumin can help ensure that TGF- $\beta$ 1 reaches the wound area where it is most needed. Albumin can release TGF- $\beta$ 1 slowly into the wound area, thus ensuring that TGF- $\beta$ 1 is available in optimal concentrations for the wound healing process. Several studies have shown that albumin can increase the bioavailability of TGF- $\beta$ 1 and accelerate wound healing. Topical albumin increases TGF- $\beta$ 1 levels and accelerates wound closure in mice with diabetic wounds. Oral albumin increases TGF- $\beta$ 1 levels and strengthens granulation tissue in rabbits with burn wounds. Topical albumin increases TGF- $\beta$ 1 levels and accelerates wound healing in patients with burns. Albumin plays an important role in increasing the bioavailability of TGF- $\beta$ 1 and accelerating wound healing. Its mechanism of action involves binding to TGF- $\beta$ 1, delivering it to the wound area, and releasing it slowly. Further research is needed to confirm the effectiveness of albumin in different types of wounds

and patient conditions.<sup>19-21</sup>

Albumin can activate the TGF- $\beta$ 1 signaling pathway in cells, which triggers the production of TGF- $\beta$ 1. This signaling pathway involves activation of the TGF- $\beta$ 1 receptor and signal transduction into the cell. Albumin can increase TGF- $\beta$ 1 gene expression in cells, leading to increased TGF- $\beta$ 1 production. The TGF- $\beta$ 1 gene encodes the TGF- $\beta$ 1 protein, and increased expression of this gene produces more TGF- $\beta$ 1 protein. Albumin can increase the stability of TGF- $\beta$ 1 mRNA, leading to increased TGF- $\beta$ 1 production. TGF- $\beta$ 1 mRNA is an RNA copy of the TGF- $\beta$ 1 gene, and higher mRNA stability means more TGF- $\beta$ 1 protein can be produced. Albumin can bind to the TGF- $\beta$ 1 receptor and help activate it. This is important because activation of the TGF- $\beta$ 1 receptor is required to initiate the TGF- $\beta$ 1 signaling pathway. Albumin can increase the expression of the TGF- $\beta$ 1 receptor on target cells. This is important because the more TGF- $\beta$ 1 receptors expressed by a cell, the more sensitive the cell is to TGF- $\beta$ 1. Albumin can induce the activation of TGF- $\beta$ 1 signaling pathways, such as the Smad pathway and the MAPK pathway. This signaling pathway is important for transducing TGF- $\beta$ 1 signals into cells and triggering cellular responses necessary for wound healing.<sup>18-21</sup>

Striatin, the main protein in snakehead fish skin, has several mechanisms that can trigger TGF- $\beta$ 1 activity and increase cell proliferation, which is important for wound healing. Striatin can stimulate the proliferation of fibroblasts, cells that play an important role in producing collagen and extracellular matrix. Collagen is the main structural protein of connective tissue which provides strength and stability to wounds. Striatin can activate the mitogen-activated protein kinase (MAPK) signaling pathway and the PI3K/Akt pathway, which play a role in the regulation of cell proliferation. Striatin can increase the expression of growth factors, such as epidermal growth factor (EGF) and transforming growth factor- $\alpha$  (TGF- $\alpha$ ), which also promote cell proliferation. Striatin can increase TGF- $\beta$ 1 expression in cells involved in wound healing, such as fibroblasts,

endothelial cells, and inflammatory cells. Striatin may increase the bioavailability of TGF- $\beta$ 1 by protecting it from enzymatic degradation. Striatin can activate TGF- $\beta$ 1 signaling pathways, such as the Smad pathway and MAPK pathway, which enhances cell response to TGF- $\beta$ 1. Several studies have shown that striatin can increase cell proliferation and TGF- $\beta$ 1 activity. Striatin increases human fibroblast proliferation and increases TGF- $\beta$ 1 expression. Snakehead fish extract containing striatin increases cell proliferation and TGF- $\beta$ 1 activity in diabetic rat wounds. Snakehead fish extract containing striatin increases cell proliferation and accelerates wound healing in patients with burns. Striatin has several mechanisms that can trigger TGF- $\beta$ 1 activity and increase cell proliferation, which is important for wound healing. Striatin may be a promising therapeutic candidate for improving wound healing, especially in chronic, difficult-to-heal wounds.<sup>22-24</sup>

## 5. Conclusion

The results of this study suggest that TGF- $\beta$ 1 expression is positively correlated with dose. This finding has potential implications for understanding the role of TGF- $\beta$  in various biological processes and for developing therapeutic strategies targeting TGF- $\beta$  signaling pathways.

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