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## REVIEW ARTICLE

# POTENTIAL OF SNAKEHEAD FISH (*OPHIOCEPHALUS STRIATUS*) IN ACCELERATING WOUND HEALING

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### Abstract

Snakehead fish (*Ophiocephalus striatus*) (SF) is a type of fish that lives in fresh water and is widely known by the public. The properties and uses of SF have been scientifically proven to increase albumin levels and immune system as well as speed up the process of post-operative wound healing. The nutritional content of SF consists of albumin protein, amino acids, unsaturated fatty acids and minerals. Bioactive compounds that play a role in accelerating the wound healing process are albumin, glycine, and zinc (Zn). Wound healing is very dependent on the biochemical processes that occur on the skin involving intrinsic and extrinsic factors. This healing process will be accelerated with the help of dried SF extract which is designed in topical form such as cream or gel. Among albumin, glycine and Zn are important for wound healing because this protein is able to bind Zn and carry it in blood plasma. Zn deficiency reduces the wound healing process. Because of this nutrient, and other vitamins, it is present in SF extract so that it can trigger the formation of Endothelial Progenitor Cells (EPC) and accelerate wound healing. The presence of Zn in SF extract is likely to be a key factor playing a role in wound healing and also increases the appetite of children. Zn is an important mineral in the structure and function of cell membranes. Zn supplementation can limit membrane damage which is caused by free radicals during inflammation. Furthermore, Zn is also involved in the immune system, from the defense system by the skin to the regulation of genes in lymphocytes.

**Keywords:** Albumin, glycine, snakehead fish, wound, zinc.

## INTRODUCTION

Indonesia is an archipelago that is rich in natural materials from marine plants and marine animals. One of them is snakehead fish (SF) (*Ophiocephalus striatus*) which is usually found in Limboto Lake, Gorontalo Province. Snakehead fish (SF) is one of the freshwater fish and brackish water which is also included in the type of fishing fish that is commonly found in rivers, swamps, lakes and waterways down to the rice fields<sup>1</sup>. The efficacy and use of SF has been scientifically proven to increase albumin levels and endurance as well as speed up the process of post-operative wound healing<sup>2</sup>. In general, traditional medicine that has been carried out by the Indonesian people, especially the Gorontalo people, by steaming of SF to obtain the extract then drunk to patients who are malnourished or postoperative wounds after giving birth. Basically the administration of SF water extract to patients is less favored due to the smell so that many patients do not like it. Therefore, researchers have previously made it in the form of capsules that are drunk to post-surgical wound patients and the topical

effect on wound skin has been done pre-clinically on experimental animals showing a cream concentration of 2% dry extract of SF provided a wound healing process which was rapid growth within 3 days compared to other cream concentrations<sup>3</sup>. During the current crisis, imported serum albumin used often burdens the patient's costs. For one surgery, the use of this serum reached three times 100 ml. From the results of Suprayitno's research (2003) stated it turned out that snakehead fish in Indonesia have high albumin and amino acids content compared to other freshwater fish such as catfish, tilapia, goldfish, carp, gourami and so on<sup>4</sup>. Taslim's research results (2005) showed that the administration of SF water extract as much as 100 ml every day for 3 days increased levels of albumin and total protein of patients. The average increase in albumin levels was 0.7 g/dl/day compared to the control group<sup>5</sup>. The results of Hidayanti's research (2006) showed that administration of albumin for wound healing in the form of SF capsules daily for 5 days on hypo-albumin of post-operative patients at Wahidin Sudirohusodo Hospital, Makassar had been able to increase albumin levels by an average of 0.74

g/dl/day followed by improvement in nutritional status compared to the control group<sup>6</sup>. The effectiveness of snakehead fish as a wound healing material is influenced by the high content of certain amino acids, such as glycine and unsaturated fatty acids such as omega-3 which are believed to be involved in promoting wound healing through the initiation of a series of reactions involving remodeling-collagen, wound re-epithelialization and induction of wound contraction. Besides that, SF extract also has the ability to cause proliferation of mesenchymal cells and maintain cell viability for use as a biochemical and healing promoter that is not limited to skin wounds<sup>11</sup>.

Therefore, in this review the author will discuss the potential of snakehead fish in accelerating the wound healing process in terms of biochemical compounds which are contained by snakehead fish and pharmaceutical dosage forms which are derived from snakehead fish.

### The contents of snakehead fish

Snakehead fish are known to contain albumin and other types of protein that are very important for health. The use of SF for treatment has been carried out in several areas. In South Sulawesi, SF is consumed by women who have just given birth. By consuming SF, it is hoped that women who give birth quickly recover and produce plenty of breast milk for their baby's needs.

In the Toraja and Enrekang areas, SF was given long ago to children because it is believed to be able to increase children's immunity<sup>7</sup>. Based on the SF content table<sup>8</sup>, the amount of SF nutrition per 100 grams of material can be seen in Table 1.

**Table 1: Number of consumption of SF per person per day which is needed by the body.**

Age group	Protein (g)	SF (g)
0- 6 bulan	10	39.68
7 - 11 bulan	16	63.49
1- 3 bulan	25	99.20
4- 6 tahun	39	154.76

Researchers in Southeast Asia, especially Malaysia and Indonesia, have proven that SF is one of the important fish for human health. SF powder protein concentrate has been shown to be able to accelerate the healing of infectious diseases and increase endurance due to its protein albumin content<sup>9</sup>.

Albumin is the main fraction of elliptical plasma proteins and has a molecular weight and isoelectric pH that varies by species. The molecular weight of human plasma albumin is 69,000, egg albumin 44,000, and in mammalian meat 63000<sup>10</sup>. The isoelectric pH of albumin varies between 4.6 (egg albumin) to 4.9 (serum albumin). Mature human albumin consists of a polypeptide chain. Albumin is rich in lysine amino acids, arginine, glutamic acid, and aspartic acid<sup>11</sup>. The nutritional content of SF can be seen in the Table 2.

### Wound

Surgery is all treatments that use an invasive method by opening or displaying the part of the body to be treated. The opening of this part of the body is generally made by making an incision, after the part to be treated displaying, repairs are done which ends with

the closure and suturing of the wound<sup>12</sup>. As one form of therapy, surgery is quite unique. Patients, who are already in a state of stress due to illness, will get additional stress or trauma and the possibility of sepsis while undergoing surgical treatment.

**Table 2: The nutritional contents of SF.**

S. N.	Nutritional content	The amount of materials
1	Protein	85.6 %
2	Albumin	30.2%
3	Lipids	5.1%
4	Omega-3	2.03%
5	Omega-6	2.11%
6	Omega-9	0.92%
7	Vitamin A	1500 IU/100 g
8	Vitamin B1	0.9 mg/100 g
9	Vitamin B2	1.11 mg/100 g
10	Vitamin B6	0.70 mg/100 g
11	Vitamin B12	0.76 mg/100 g
12	Vitamin E	9.11 mg/100 g
13	Vitamin D3	51.5 mg/100 g
14	Calcium (Ca)	186 mg/100 g
15	Phosphor (P)	126 mg/100 g
16	Magnesium (Mg)	39 mg/100 g
17	Seng (Zn)	3.0 mg/100 g
18	Anti-bacteria Ig+	2.11 IU/g
19	Arachidonic acid	20.11 mg/100 g

The bad influence of stress on nutrition will also multiply considering that healing is always related to nutritional status. Metabolic changes, assessment of nutritional status, nutritional needs, and nutritional support must be considered at every surgery<sup>13</sup>. The surgical process is deliberately made into a wound so that stress occurs causing metabolic changes due to complex endocrine reactions, as a result of the wound healing process and many related factors. Wound healing can be disrupted due to endogenous and exogenous factors. If wound healing means complications or disruption occurs in the results of surgery, thus the state of malnutrition will affect the wound healing process<sup>14</sup>. Injuries to the body can cause a whole catabolic process associated with weight loss, anorexia, and fatigue with decreased activity and many clinical complaints that are associated with metabolic responses<sup>15</sup>. The metabolic response of injuries which is caused by surgical procedures can cause loss of nitrogen from the body. Negative Nitrogen balance is caused by increased excretion of urea and other nitrogen products through urine. Likewise, the number of open wounds (such as burns) where there is a loss of protein in the tissue<sup>16</sup>. Nutritional disorders in post-surgical patients are caused by low nutrient intake so that nutrient stores in the body are used to meet physiological needs. If this condition is not corrected and continues to continue it will result in biochemical changes in the body characterized by low levels of some nutrients in the body such as hemoglobin, serum albumin, vitamin A and others. If this situation continues, over time the nutrient deposits will run out and there will be a decrease in tissue should be which is marked by weight loss. This makes it easier to get infected or the infection becomes more severe<sup>17,18</sup>. Trauma will produce a neuroendocrine response that

results in changes in hormone levels that are greatly changed from those observed in prolonged starvation. Cortisol, glucagon, catecholamines, epinephrine and norepinephrine increase in proportion to the degree of trauma.

**Table 3: The contents of amino acids in SF.**

S. N.	Amino acids	The amount of materials
1	Aspartate	1.04 g/100 g
2	Glutamate	15.0 g/100 g
3	Serine	1.0 g/100 g
4	Glycine	1.11 g/100 g
5	Alanine	2.11 g/100 g
6	Leucine	1.60 g/100 g
7	Isoleucine	0 g/100 g
8	Valine	2.11 g/100 g
9	Tryptophan	3.0 g/100 g
10	Hydroxy Proline	8.10 g/100 g
11	Proline	1.0 g/100 g
12	Phenylalanine	0.81 g/100 g
13	Histidine	1.0 g/100 g
14	Cysteine	1.07 g/100 g
15	Lysine	1.46 g/100 g
16	Tyrosine	0.92 g/100 g

This hormone causes muscle proteolysis (cortisol), glycogenesis and increased gluconeogenesis and lipid oxidation<sup>19</sup>. Injury is the loss or damage of some body tissue. This situation can be caused by sharp or blunt trauma, changes in temperature, chemicals, explosions, electric shock, or animal bites<sup>20</sup>. The process that then occurs in this damaged tissue is wound healing which can be divided into three phases, namely the inflammatory, proliferation, and intermittent phases which are remodeling of the tissue.

### 1. Inflammatory phase

The inflammatory phase lasts from the time of injury until approximately the fifth day. Disconnected blood vessels in the wound will cause bleeding and the body will try to stop it by vasoconstriction, shrinkage of the end of broken vessels (retraction), and hemostatic reactions. Hemostasis occurs because platelets that come out of the blood vessels stick together, and together with the fibrin tissue that forms, clots the blood that comes out of the blood vessels and inflammatory reaction occurs<sup>21</sup>. Mast cells in connective tissue produce serotonin and histamine which increase capillary permeability resulting in fluid exudation, inflammation of inflammatory cells, accompanied by local vasodilation which causes edema and swelling. Clinical signs and symptoms of inflammation reaction become clear in the form of reddish color due to dilated capillaries (rubor), temperature of inflammation cells, accompanied by local vasodilation causing edema and swelling. This phase is also called the slow phase because the reaction of the formation of new collagen is small and the wound is only linked by very weak fibrin<sup>22</sup>.

### 2. Proliferation Phase

The proliferation phase is also called the fibroplasia phase because stands out is the fibroblast proliferation process. This phase lasts from the end of the inflammatory phase until approximately the third week.

Fibroblasts are derived from undifferentiated mesenchymal cells, producing muco-polysaccharides, glycine amino acid, and proline which are the basic ingredients of collagen fibers that will link the wound edges. In this phase fibers are formed and destroyed again to adjust to the tension in the wound that tends to shrink. This trait, along with the contractile nature of myofibroblasts causes traction at the wound edges. At the end of this phase the strength of the wound strain reaches 25% of normal tissue. Later, in the process of ending the strength of collagen, fibers increases due to intramolecular and intermolecular bonds. This process only stops after the epithelium touches each other and closes the entire wound surface. With the wound surface closed, the process of fibroplasia by forming granulation tissue which will also stop and the maturation process and begin in the interim phase<sup>21,23</sup>.

### 3. Interim Phase

In this phase, the maturation process consists of re-absorption of excess tissue, shrinkage in accordance with gravity, and finally re-forming of newly formed tissue. This phase occur the last for months and is declared over when all signs of inflammation have disappeared. The body tries to normalize everything that has become abnormal due to the healing process. Udem and inflammation cells are absorbed, young cells mature, new capillaries close and are reabsorbed, excess collagen is absorbed and the rest shrinks according to the existing strain. During this process scar tissue is produced which is pale, thin and limp and easy to move from the bottom. Maximum shrinkage is seen in the wound. At the end of this phase, the appearance of skin injury is able to withstand a stretch of approximately 80% of normal skin ability. This is achieved approximately 3-6 months after healing. The appearance of a bone injury (broken bone) takes a year or more to reach normal tissue histologically or in a form<sup>16,21</sup>.

Wound healing can be disrupted by causing from within the body itself (endogenous) or outside the body (exogenous). The most important endogenous causes are coagulation and immune system disorders. All blood clotting disorders will inhibit wound healing because hemostasis is the starting point and basis of the inflammatory phase. Immune system disorders will inhibit and change the body's reaction to injury, tissue death, and contamination. When the immune system, both cellular and humoral is disrupted, then cleaning of contaminants and dead tissue and containment of infection do not go well. In addition to viral infections and poor general conditions, the immune system is affected by malnutrition due to hunger, malabsorption, and also by deficiencies essential amino acids, minerals and vitamins, as well as disorders of food metabolism, for example in liver disease<sup>3,21</sup>.

Various factors can affect wound healing, among others:

#### 1. Intrinsic factor

##### a. Adverse local conditions in the wound

Adverse local conditions at the site of injury can be excessive exudate, dehydration, wound infection, recurring trauma, decreased wound temperature, poor blood supply, edema, local hypoxia, necrotic tissue and

extensive tissue peeling, excessive metabolic waste products and the presence of foreign object<sup>24</sup>.

#### **b. General pathophysiological factors**

Pathophysiological factors include anemia, decreased resistance to infections, metabolic and endocrine disorders, malnutrition and cardiovascular disorders. These factors can affect local conditions that are detrimental to the wound site<sup>24</sup>.

#### **c. Normal physiological factors related to age**

This can affect the general pathophysiological factors in patients<sup>24</sup>.

### **2. Extrinsic factors**

#### **a. Improper wound management**

Improper wound management can be influenced by inaccurate wound assessment, use of topical agents and inappropriate primary dressing products, careless dressing replacement techniques, and staff negative attitudes towards treatment and healing. These factors can affect adverse local conditions in wound site.

#### **b. Adverse effects of other therapies**

The detrimental effects of other therapies can be cancer chemotherapy, prolonged high steroid doses and radiation therapy. This factor can also affect local conditions that affect the site of the wound.

#### **The role of snakehead fish for health**

From the above review of the wound, it can be seen that the wound can be caused by many factors, where the role of SF has been used by the community to accelerate the healing process of various types of wounds, especially post-operative wounds. This is because SF contains bioactive compounds accelerating wound healing such as amino acids (glycine), zinc minerals (Zn), and unsaturated fatty acids such as omega-3, omega-6 and omega-9.

Wound healing is very likely to require protein, among other important substances, as a basis for the formation of collagen tissue. The study showed a significant relationship between serum albumin administration and duration of wound healing ( $p=0.001$ ). Albumin has functions as a binding and transporting agent, regulating osmotic pressure, inhibiting platelet formation and anti-thrombosis, increasing cell permeability, and antioxidant<sup>11,23</sup>.

Zn deficiency is associated with changes in the immune system such as decreased B and T cell function, hypersensitivity reactions, phagocytosis, and cytokine production. Zn deficiency also causes disruption of microbial destruction and wound healing process. Giving Zn per oral effect on alkaline phosphatase increases and accelerates the healing process of surgical wounds<sup>16</sup>. This can happen because the data show that Zn plays an important role in protein synthesis and in cell multiplication. The human body consists of connective tissue made of protein, so to build and maintain the integrity of the connective tissue required Zn<sup>25</sup>. Zn deficiency is also associated with impaired sense of taste. Children who have low Zn content and can cause abnormalities in their sensory hair. This can be prevented and cured by zinc supplementation<sup>26</sup>.

Besides that, SF is now widely studied by researchers in pharmaceutical dosage forms and had been done by the author and published. For example:

1. Dried extract of SF in cream dosage form to accelerate the wound healing process<sup>3</sup>.
2. Dried extract of SF in the form of a double emulsion syrup to increase the immune system<sup>27</sup>.
3. Dried SF powder in nanoemulsion dosage form to accelerate the healing of open wounds<sup>28</sup>.
4. Dried powder of SF in nanoemulgel dosage form to accelerate the healing of burns<sup>29</sup>.
5. Dried SF powder in the form of injection liposomes for the treatment of breast cancer chemotherapy<sup>30</sup>.

Therefore, from all the results of research that had been done by the author, it is expected to contribute to developing natural resources, especially the potential of snakehead fish as a bioactive compound that is not toxic in the human body.

### **CONCLUSIONS**

The potential of snakehead fish in accelerating the wound healing process greatly helps improve the degree of public health. This is related to the nutritional content of snakehead fish such as albumin, glycine and Zn. Among albumin, glycine and Zn are important for wound healing because this protein is able to bind Zn and carry it in blood plasma. Zn deficiency reduces the wound healing process. Because this nutrient and other vitamin are present in snakehead fish extract so that it can trigger the formation of Endothelial Progenitor Cells (EPC) and accelerate wound healing. The presence of Zn in SF extract is likely to be a key factor that plays a role in wound healing and increasing children's appetite. Zn is an important mineral in the structure and function of cell membranes. Zn supplementation can limit membrane damage which is caused by free radicals during inflammation. Furthermore, Zn is also involved in the immune system, from the defense system by the skin to the regulation of genes in lymphocytes.

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### **AUTHOR'S CONTRIBUTION**

**Tungadi R:** Writing original draft, review, methodology, data curation, literature survey, editing.

### **DATA AVAILABILITY**

The data and material are available from the corresponding author on reasonable request.

### **CONFLICT OF INTEREST**

No conflict of interest associated with this work.

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