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Effectiveness of Snakehead Fish Extract on Tooth Extraction Wound Healing

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A B S T R A C T

Tooth extraction can cause open wound in the oral cavity, if not handled properly it can cause complications such as bleeding, infection and delayed wound healing. Wound healing is a biological process associated with tissue growth and regeneration. The wound healing process can be accelerated by administering chemicals that can affect the inflammatory, proliferative and remodeling phases. One of them is by giving snakehead fish extract. The extract contains albumin, copper and zinc which play an important role in the wound healing phase. The purpose of writing this review article is to explain the mechanism of snakehead fish extract in accelerating the healing of tooth extraction wounds. Several studies have revealed that snakehead fish extract affects pro-inflammatory cytokines in helping the wound healing process and significantly helps increase the number of fibroblast cells in tooth socket wounds, so that the healing process can take place more quickly. Based on this, it can be concluded that snakehead fish extract has the potential to accelerate the healing of tooth extraction wounds.

1. Introduction

The tooth extraction rate in Indonesia is relatively high. According to Riset Kesehatan Dasar 2018, the prevalence of dental and oral health services for tooth extraction in Indonesia is 7.9%, which is around 43,996 cases.[1] Tooth extraction is a minor surgical procedure that functions to remove the tooth from its socket, causing an open wound in the oral cavity, which if not treated properly can cause complications such as bleeding, infection, and delayed wound healing.[2] Even though the incidence of disruption of the wound healing process after extraction is low, the impact it can have is quite large, causing pain, unpleasant odor, and discomfort, thereby reducing the productivity of the patient.[3,4]

Wound healing is a complex process involving cellular and biochemical responses both locally and systemically, and there are several overlapping phases, namely the phases of hemostasis, inflammation, proliferation, and remodeling.[5] In the hemostasis phase, the wound response occurs so that the blood vessels themselves constrict and secrete platelets to form a stable clot that seals the damaged blood vessels. The inflammatory response is the second phase that occurs since the blood vessels leak and expel plasma and neutrophils into the tissues. Inflammation lasts up to four days after the wound and is characterized by erythema, swelling, and heat accompanied by fever. In the proliferation phase, which lasts for 4 to 21 days, angiogenesis, collagen tissue deposition, granulation tissue formation,

wound contraction, and epithelization occur. In the remodeling phase, the healing process involves remodeling and realignment of the collagen tissue to produce greater tensile strength.[6]

Several researchers state that adequate nutrition during the wound-healing period can reduce the possibility of complications and can accelerate the wound-healing process. Along with the development of the world of medicine, natural resources become an alternative to chemical treatment materials. Drugs derived from natural resources are generally considered safer than synthetic chemical drugs because they have relatively fewer side effects than synthetic chemical drugs.[7] One of the natural resources that has been used to accelerate wound healing is snakehead fish extract (*Channa striata*).

Snakehead fish are often found in Indonesia, such as Sumatra, Java, and South Kalimantan. Snakehead fish is commonly known as "Kutuk" in Java, "Haruan" in Malay and Banjar, "Bogo" in Sunda.[8] The use of snakehead fish and its products, empirically in the community, apart from being a source of animal protein, is also used as an alternative therapy to accelerate wound healing of post-operative wounds, and reduce pain, increase endurance, increase albumin and hemoglobin levels, speed up the healing process of diseases such as cancer and diabetes.[9]

The role of snakehead fish extract in wound healing is to induce cell proliferation and platelet aggregation and have anti-nociceptive effects.[8,10] This mechanism occurs because snakehead fish extract contains albumin, Zn, Cu, and Fe, which can induce fibroblast proliferation. The main ingredient in snakehead fish is albumin. Albumin can increase fibroblast proliferation, thereby increasing collagen synthesis, accumulation, and remodeling, accelerating the healing process in wounds.[11] This literature review will discuss the role of snakehead fish extract in healing tooth extraction wounds.

Tooth extraction

Tooth extraction is a minor surgical procedure performed by a dentist to remove the tooth from its socket.[12] The ideal tooth extraction is the painless extraction of a whole tooth or tooth root with minimal trauma to the tissue supporting the tooth so that the extraction scar can heal perfectly. Tooth extraction is a procedure for removing a tooth and its roots from the alveolar bone socket using forceps, an elevator, or a transalveolar approach (surgery).[13]

The indications for tooth extraction are periodontal disease, periodontal periapical or abscesses, nonrestorable caries, pulpal necrosis, remaining tooth roots, fractured teeth, and failed root canal treatments with the persistence of periapical cysts or granulomas, impacted teeth, supernumerary teeth, or to facilitate orthodontic or prosthodontic rehabilitation.[5] Caries and periodontal disease remain common reasons for tooth extraction even though they are prevented, especially in developing countries. Dental caries and periodontal disease are the main reasons for tooth extraction of gender, age, behavior, and socioeconomics.[14]

The consequence of routine tooth extraction could lead to dentoalveolar diseases, which can cause tooth loss. The various complications of surgical procedures are postoperative bleeding, delayed wound healing, residual bony spicules, and nerve paresthesia. Complications of extractions can be multifactorial and are attributed to the health status of the patient, habits, medical history, and systemic and local factors.[5] Following routine dental extractions, complications, such as pain, inability to work, discomfort, and delayed healing of the socket, can occur. In systemic conditions like diabetes, decreased synthesis of collagen and decreased angiogenesis can cause impaired wound healing. Progressive retardation of the immune system in human immunodeficiency virus infection and decreased oxygen supply in chronic obstructive pulmonary disease, Cushing's syndrome, and malnutrition are

also implicated in delayed wound healing.[15]

Tooth extraction wound healing

Tooth extraction initiates the same sequence of hemostasis, inflammation, proliferation, and remodeling as seen in prototypic skin or mucosal injury. As previously mentioned, sockets heal by secondary intention, and it can take months before the socket heals to the point that it is difficult to differentiate from the surrounding bone when viewed radiographically. When a tooth is removed, the remaining empty socket consists of cortical bone (radiographic lamina dura) covered by the torn periodontal ligament, with a rim of oral epithelium (gingiva) remaining at the crown. The socket fills with blood, which clots and seals off the socket from the oral environment.[5]

The inflammatory stage occurs in the first week of healing. White blood cells enter the socket to remove contaminating bacteria from the area and begin to break down debris, such as bone fragments left in the socket. Fibroplasia also begins in the first week, with inward growth of fibroblasts and capillaries. The epithelium migrates down the socket wall until it reaches a level where it contacts the epithelium from the other side of the socket or meets the layer of granulation tissue (i.e., tissue filled with many capillaries and immature fibroblasts) beneath the blood clot. Where the epithelium can migrate. Finally, during the first week of healing, osteoclasts accumulate along the crestal bone. The second week is characterized by an abundance of granulation tissue that fills the socket. Osteoid deposits begin along the alveolar bone lining the socket. In smaller sockets, the epithelium may be completely intact at this point. The process that begins in the second week continues in the third and fourth weeks of healing, with epithelialization of most of the socket completed by this time. Cortical bone continues to resorb from the apex and walls of the socket, and new trabecular bone is laid over the socket. Not until 4 to 6 months after extraction is the cortical bone lining the socket usually completely absorbed; this is recognized radiographically by distinct loss of the lamina dura. As the bone fills the socket, the epithelium moves toward the crest and eventually becomes aligned with the adjacent crest gingiva. The only visible remnant of the socket after 1 year is the edge of fibrous tissue (scar) remaining on the edentulous alveolar ridge.[5]

Snakehead fish (*Channa striata*)

Snakehead fish (*Channa striata*) is a freshwater fish that has high nutritional value. This fish comes from tropical areas such as Asia and Africa. Snakehead fish can easily be found in various open waters in Indonesia, especially on the islands of Java, Sumatra, Kalimantan, Sulawesi, Bali, Lombok, Flores, Ambon, and Maluku, with various local names. Local names for snakehead fish include Curse (in Java), Kocolan (in Betawi), Aruan or Haruan (in Malaysia and Banjarmasin). In English, it is generally known as snakehead, snakehead murrel, chevron snakehead, or striped snakehead.[16]

Snakehead fish usually live in swamps or lakes and may inhabit dirty water, ditches, rice fields, and ponds, and are even abnormally able to withstand drought. This fish can survive the dry season by burying itself in the mud, breathing anaerobically, and can jump onto dry land. As predators and carnivores in nature, these fish prey on small fish, frogs, young turtles, and even ducklings around them.[16]

Snakehead fish is a type of freshwater fish from the genus *Channa* which has economic value and has long been used as a consumption fish. The *Channa* genus consists of 4 species, namely *Channa striata* (snake fish), *Channa gachua* (bakak fish), *Channa micropeltes* (toman fish), and *Channa lucius* (bujok fish).[17] Snakehead fish is classified as a carnivorous animal and also a predator. The shape is almost round and long. The back of the fish is convex, while the belly is quite flat with a snake-like head. It is dark green dorsally and cream or white ventrally and has a long,

semicircular, broad caudal fin with rounded pectoral fins. Snakehead fish also have dorsal fins and hard spines. Snakehead fish can reach lengths of up to 90-110 cm.[18]

Content of snakehead fish extract

Snakehead fish (*Channa striata*) contains albumin, which is an important type of protein that the human body needs every day, even in the wound-healing process. Snakehead fish (*Channa striata*) has the highest albumin content compared to sea fish and other freshwater fish such as catfish and gourami fish. Snakehead fish has great benefits in both the food and pharmaceutical industries.[5] Snakehead fish (*Channa striata*) contains albumin and Zn with essential amino acids, namely threonine, valine, methionine, isoleucine, leucine, phenylalanine, lysine, histidine, and arginine. As well as non-essential amino acids, including aspartic acid, serine, glutamic acid, glycine, alanine, cysteine, thyroxine, hydroxylysine, ammonia, hydroxyproline, and proline. Snakehead fish extract also has 8 types of fatty acids and two types of essential fatty acids, which are classified in the omega-6 group, such as linoleic acid and arachidonic acid.[8] The albumin content of male snakehead fish is 6.7% lower than that of female snakehead fish, which has an albumin content of 8.2%. The nutritional content contained in snakehead fish can be seen in Table 1.

Table 1. The nutritional content of snakehead fish.[9,12]

Nutrient content	Quantity
Proteins	85,6 %
Albumin	30,2%
Fat	5,1%
Omega-3	2,03%
Omega-6	2,11%
Omega-9	0,92%
Vitamin A	1500 IU/100 g
Vitamin B1	0,9 mg/100 g
Vitamin B2	1,11 mg/100 g
Vitamin B6	0,70 mg/100 g
Vitamin B12	0,76 mg/100 g
Vitamin E	11 mg/100 g
Vitamin D3	51,5 mg/100 g
Calcium (Ca)	186 mg/100 g
Phosphorus (P)	126 mg/100 g
Magnesium (Mg)	39 mg/100 g
Zinc (Zn)	3,0 mg/100 g
Antibacterial Ig+	2,11 IU/g
Arachidonic acid	20,11 mg/100 g

The benefits of snakehead fish

Snakehead fish has benefits as an anti-inflammatory, antipyretic, antinociceptive, antihyperglycemic, antimicrobial, and neuroregenerative and improves the wound healing process. Snakehead fish is used by the community empirically to accelerate the healing process of various types of wounds, especially postoperative wounds. Snakehead fish (*Channa Striata*) contains bioactive compounds that accelerate wound healing such as albumin, amino acids (glycine), zinc (Zn), iron (Fe), and Cuprum (Cu). Wound healing requires protein, especially albumin, among other important substances, as the basis for the formation of collagen tissue. Albumin functions as a binding and transport agent, regulates osmotic pressure, formation, and

anti-thrombosis, increases cell permeability, acts as an antioxidant, and increases the aggregation and proliferation of fibroblast cells. Snakehead fish are used in the medical world, namely as a wound healer, by taking oil from the snakehead fish. The content of bioactive compounds contained in snakehead fish can help the wound healing process.[6,9,10,12]

The role of snakehead fish in wound healing

Snakehead fish contain compounds such as albumin, Zn, Cu, and Fe minerals, which have an important role in the process of tissue synthesis and wound healing.[10] Albumin in the inflammatory phase plays a role in regulating osmotic pressure in the blood and almost 50% of plasma proteins. When injured, the skin will show signs of inflammation in the form of hydrostatic pressure disturbances, where intracellular fluid will enter the cells due to differences in concentration inside and outside the cells, causing the cells to swell. In this condition, albumin is needed to maintain osmotic pressure inside and outside the cells so that the swelling does not get worse and the wound healing process can continue to the next stage, namely the proliferation phase. The inflammatory phase itself has characteristics such as pain (dolor), heat (kalor), redness (rubor), swelling (tumor), and loss of function (functiono laesa).[5,12]

In addition, in the inflammatory phase, albumin works by reducing the production of pro-inflammatory cytokines such as TNF-a, IL-1, and IL-6, which are associated with increased apoptosis or cell necrosis. An increase in the number of pro-inflammatory cytokines can increase the regulation of I-NOS (Inducile Nitric Oxide Synthase), which triggers the premature aging of fibroblasts and delays epithelial cell proliferation. In addition, albumin can reduce MMP-8 levels so that collagen degradation and tissue damage can be minimized. Albumin also plays a role as an antioxidant through the mechanism of scavenging free radicals and scavenging ROS. When tissue injury occurs, damaged cells will produce reactive oxygen species (ROS) in the initial phase of wound healing, where antioxidants are needed to ward off free radicals and speed up wound closure.[19]

As a part of the wound healing process, antimicrobial activity is equally important. The antimicrobial properties of the skin and intestinal mucus of different Channa sp., namely, C. striatus, Channa micropeltes, Channa marulius, Channa punctatus, and Channa gachua have been studied by the CARE research team. The investigation showed a broad spectrum of antibacterial activity of skin mucus against Aeromonas hydrophila, Pseudomonas aeruginosa, and Vibrio anguillarum.[20] Albumin synergizes with Zn for cell development and the formation of new cell tissue. Zn is involved in the hemostatic process, which interacts with platelets and plays a role in antibody production and immune cell function. Zn plays an important role in the proliferation process of inflammatory cells and modulates inflammation to limit membrane damage caused by free radicals during inflammation.[6]

In the proliferation phase, albumin plays a role in increasing fibroblast proliferation, resulting in increased synthesis, accumulation, and remodeling of collagen. Albumin induces EGFR expression by activating ERK1/2 and upregulating NF-κB. EGFR plays an important role in the wound healing process by stimulating tyrosine kinase activity which activates gene transcription, DNA synthesis, and cell proliferation. EGFR also plays an important role in regulating the expression of TGF-β, which plays an important role in wound healing in the inflammatory phase, stimulation of angiogenesis, and proliferation of fibroblasts.[8,19]

Albumin can increase fibroblast proliferation, thereby increasing collagen synthesis, accumulation, and remodeling, accelerating the healing process in wounds.[21] This is in line with research conducted by Siswanto et al. in 2016, which proved that administering snakehead fish extract orally at a concentration of 25%, 50%, and 100% to the oral

mucosal wounds of Wistar rats could increase the number of fibroblasts when compared to the control group, and increased the number of fibroblasts compared to the control group. The higher the concentration, the more the number of fibroblasts will increase.[9] Another study by Oentaryo et al. showed that oral administration of snakehead fish extract for healing lower lip mucosal wounds at concentrations of 25%, 50%, and 100% increased the number of fibroblasts when compared to the control group.[9,12]

Research conducted by Atmaja et al. in 2019 also proved that snakehead fish extract gel on post-extract socket wounds with a concentration of 100% also increased the number of fibroblasts when compared to the control group given CMC-Na.[12] Increased fibroblast proliferation causes faster tissue structure repair during the wound healing process. In addition, albumin can stimulate neutrophils, monocytes, and macrophages to release proinflammatory cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), and fibroblast growth factor (FGF), which are involved in the activation of fibroblasts and cells. Epithelium. PDGF stimulates fibroblast function and collagenase expression. TGFβ controls regulatory signals of extracellular matrix deposits, increasing matrix protein production and downregulating protease enzymes.[12]

The role of albumin in the maturation phase is as a basic material for the formation of collagen. Collagen rapidly developed into the main factor forming the matrix. Collagen fibers are initially randomly distributed to form crosses and aggregate into fibril bundles, which slowly cause tissue healing and increase the stiffness and tensile strength of the collagen fibers. The return of tensile strength will occur slowly due to the continuous deposition of collagen tissue and remodeling of collagen fibers to form larger collagen bundles. Collagen remodeling during scar tissue formation depends on the continuous process of collagen synthesis and catabolism. The maturation stage begins on the 21st postoperative day and can continue for years. Other nutrients besides albumin contained in the water phase of snakehead fish extract are water-soluble vitamins such as vitamin C and water-soluble minerals. Minerals such as zinc play a role in strengthening new tissue, while vitamin C plays a role in the formation of collagen.[23]

Zinc plays a major role in regulating every phase of the wound healing process, starting from membrane repair, oxidative stress, coagulation, inflammation and immune defense, tissue re-epithelialization, and angiogenesis to fibrosis/scar formation. In the hemostatic phase, zinc has a role in increasing platelet activity and aggregation through protein kinase C (PKC), which is mediated by tyrosine phosphorylation of platelet proteins (Peiheulien-2018) to form fibrin clots. If zinc levels are low, it can cause a decrease in the ability to aggregate platelets, resulting in elongation bleeding time. During the proliferation and maturation phase, Zn is needed for collagen synthesis. The Zn element is also needed for the proliferation of fibroblasts and keratin cells and to accelerate the process of re-epithelization.[6,16]

Zinc is a component that plays a role in the synthesis of protein, DNA, RNA, and cell proliferation. Neutrophils and macrophages require zinc to proliferate. Neutrophils work as phagocytosis of foreign substances and signal inflammatory cytokines, growth factors, and enzymes. Macrophages clean wounds through phagocytosis, secrete growth hormone, recruit fibroblasts, create the initial framework for granulation, and secrete nitric oxide, which has many functions, including vasodilation, thrombolysis, angiogenesis, and cell regulation. Zinc also influences fibroblast proliferation. Reducing the amount of zinc at the cellular level can result in a reduction in the number of fibroblasts, resulting in poor granulation and delayed wound closure.

The human body contains Zn ranging from 1.4 to 2.3g. The Zn content in plasma is about 100

mg/100mL. The Zn daily requirement for adults is 15 mg/day. The Zn content of snakehead fish extract is 3.43mg/100mL. Giving 30mL/kg/day of the extract as part of the diet contributes 31.98% of the recommended food intake. Thus, the extract is a fairly good source of Zn.[16] Izzati 2014, reported that the Cu content in snakehead fish was 0.447 mg/L of CU. Copper plays a role in cell growth and replication, which can trigger fibroblast proliferation in areas undergoing the healing process.[24]

2. Conclusion

Snakehead fish extract has the potential to accelerate the healing of tooth extraction wounds. This mechanism occurs because snakehead fish extract contains albumin, Zn, Cu, and Fe, which can induce fibroblast proliferation. The main ingredient in snakehead fish is albumin. Albumin can increase fibroblast proliferation, thereby increasing collagen synthesis, accumulation, and remodeling, accelerating the healing process in wounds.

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