REVIEW ARTICLE

The Potential Synergistic Effects of Honey and Snakehead Fish Skin (*Channa sp.*) on Burn Healing: A Narrative Review

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ABSTRACT

Objective: **The administration of antibiotics is usually used in burn healing to avoid microbial infection that causes the wound healing process's failure. However, this method potentially causes bacterial resistance, leading to prolonged wound healing. This narrative review aimed to explore the potential effects of honey and snakehead fish (*Channa sp.*) skin extract in a hydrogel preparation to accelerate burn healing.**

Discussions: **Available literature demonstrated that honey's substance possesses antimicrobial, antioxidant, and antiinflammatory properties, modulating the immune system. Snakehead fish skin is rich in protein, minerals, and collagen, supporting a faster wound-healing process. When combined in a hydrogel preparation, the 2 ingredients will potentially synergize to accelerate burn wound healing.**

Conclusion: **Snakehead fish skin and honey in hydrogel formulations potentially have a synergistic effect of healing burns. This review could be a reference for further studies regarding gel formulations and preparation methods and their direct impact on burns.**

KEY WORDS

burn, honey, hydrogel, snakehead, wound

INTRODUCTION

One of the most common global injuries is caused by burns. Its incidence and mortality are highest in the middle- and low-income countries[1)]. Burns are treated by preventing infection and allowing epithelial cell remnants to proliferate and, therefore, successfully cover the wound surface. The critical component of the regeneration of damaged tissue is collagen, a product secreted by fibroblasts[2)]. However, the burns' healing process is frequently inhibited by microorganisms[3)]. Common bacteria that inhibit wound healing are *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*. Topical antibiotics are commonly administered to treat burns. However, such a method is highly susceptible to causing bacterial resistance[4)].

During the last century, natural ingredients have received more attention in terms of exploration and reuse in this modern era, especially for such therapy as wound healing that could minimize resistance, such as honey. The use of honey has long been recognized among different civilizations, including Ancient Sumer, Ancient Egypt, Ancient Greece, and China, and mentioned in Al-Quran[5,6)]. To date, honey as a topical agent is reused in modern medicines to treat wounds and burns. The therapeutic properties of honey have been scientifically analyzed and proven in many studies *in vitro* until clinical trials for the last one hundred years[7)]. Previous studies have reported that the topical use of honey for a long time does not cause resistance but instead of the effects of antibiotics[5,8)].

Meanwhile, snakehead fish (*Channa sp.*) is commonly discovered in Asia and Africa. Particularly in Indonesia, they live in the rivers and swamps in Sumatera, Kalimantan, and Java islands[9)]. Compared to tilapia, which is widely used in Brazil for burn therapy, snakehead fish skin has a higher collagen content[10,11)]. However, snakehead fish in Indonesia is widely consumed only as food. There is the same type of collagen, type 1, as humans in snakehead fish skin[12)]. Therefore, using snakehead fish skin will give many advantages to the burns treatment since it is affordable and free from poultry or mammal diseases, and it has higher collagen content than poultry, mammals, or other fish[13)].

Thus, honey and snakehead fish skin's potential synergistic effects in treating burn wounds should be comprehensively explored. This narrative review aims to investigate honey and snakehead fish skin's potential in treating burns, emphasizing the underlying mechanisms and recent burn healing advancements.

DISCUSSION

Inhibition of wound healing process

The wound-healing process will be inhibited if influencing factors,

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including nutrients, age, and immunosuppression, are disturbed. Malnutrition impairs wound healing by prompting prolonged inflammation or reducing collagen deposits. Some nutrients, such as carbohydrates for collagen synthesis and vitamin A for epidermal growth, should be considered. Wound healing could be inhibited in elderly patients since their lack of inflammatory response or exacerbated by chronic wounds[14)].

Burns result in immunosuppression of specific and non-specific components[15)]. This condition causes rapid infection due to loss of skin integrity, resulting in microbial invasion into the body. The most common pathogen in burns is gram-positive bacteria, such as *Staphylococcus aureus*, a drug-resistant microorganism. Also, 75% of deaths are caused by infections that follow the initial resuscitation of burn victims[16)].

Although antibiotics as prophylaxis benefit the treatment of burn infection, they cause resistance to some strains of microorganisms, thus impeding treatment[16)]. Today, there are yet any ideal topical antibiotics for burns. A study indicated that some multidrug-resistant organisms (MDROs), rather than non-MDROs, are vulnerable to topical agents[17)]. Therefore, it is desirable to discover topical therapeutic agents that are efficient but do not cause resistance.

Healing properties of honey

Honey bees collect naturally sweet liquids derived from flower nectar known as honey (*Apis sp*.). The major component of honey is carbohydrates, about 60-85% of the content. The minor components comprise protein, lipids, free amino acids, phenolic compounds, vitamins, and minerals. Many factors determine the complexity of the mixture, including the flora sources, bee species, seasonal factors, and the environment[18,19)].

Fructose is the most significant fraction of carbohydrates in nearly all honey sorts[20)]. Besides, honey contains amino acids, including alanine, phenylalanine, glutamic acid, leucine, isoleucine, and tyrosine, with proline as the most[21)]. In addition, honey contains the most abundant amino acid, proline. Proline composes 50% of the total free amino acids and comes from the secretion of honeybee saliva during the transformation of nectar into honey[20)]. Meanwhile, a small number of vitamins are also contained in honey, including vitamin B complex and vitamin C. The vitamins could be preserved and maintained because of the low pH of honey[22)].

An *in vitro* study proved that commercial honey contains phytochemical compounds, including alkaloids, phenols, flavonoids, saponins, and anthraquinones[23)]. Also, there are some minerals in honey, such as potassium (K), magnesium (Mg), phosphorous (P), iron (Fe), manganese (Mn), calcium (Ca), and sodium (Na). Mineral content is different if light-colored honey ranges between 0.04% and 0.2% in dark honey[24)]. Honey reflects the plant's chemical components from which honey bees collect their food because the honey component's material depends on the soil's type and the origin of the flora[19,24)].

The role of honey components in wound healing

Osmolarity

The high osmolarity of honey inhibits bacterial growth, proliferation, and binding of water molecules. As a thick liquid, honey is a safe barrier to prevent wound infection. When the wound is applied honey, bacteria's inadequate access to water leads to dehydration and, eventually, the death of microorganisms. The osmotic pressure of honey releases the lymphatic fluid from the subcutaneous tissue to remove necrotic debris in the wound. High levels of carbohydrates such as fructose, glucose, maltose, and sucrose also play a role in honey's high osmolarity[7,25,26)]. Although osmolarity directly correlates with viscosity and antimicrobial properties, honey's antimicrobial activity does not entirely disappear when honey is diluted. Honey is efficient against *Staphylococcus aureus* because it produces hydrogen peroxide (H_2O_2), inhibiting bacterial growth[27,28)].

H_2O_2 in honey

Honey with a higher viscosity has a lower concentration of H_2O_2, whereas its maximum accumulation is found at a concentration of honey of 30-50%. Therefore, honey with a low viscosity is more effective in wound healing than highly viscous honey[29)]. When honey is watered down, it shows the ability to eradicate antibiotic-resistant pathogens[27)]. Overall, the H_2O_2 property in honey differs significantly depending on the flora and the region[8)].

In wound healing, H_2O_2 is typically unfavorable as it contributes to severe inflammatory reactions and injures the skin. However, honey could disable free iron, which catalyzes oxygen-free radicals, thus reducing the harmful effects of H_2O_2. On the other hand, the levels of H_2O_2 in honey are too low. Since honey has a high antioxidant content, the wound tissue could be protected from H_2O_2-induced oxygen radicals[30-32)]. To assist with its antimicrobial function, H_2O_2 enhances the spread of fibroblasts and angiogenesis and raises the hiring of platelets for ischemic ulcers[33)].

Immunomodulation

Honey could stimulate T- or B-lymphocytes and activate neutrophil-mediated phagocytosis. Honey activates cytokines secretion by monocytes, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), to provide an immune response to infection. TNF-α secretion could be induced by protein glycosylation. Furthermore, honey could degrade type IV collagen by stimulating matrix metalloproteinase 9 (MMP-9) during reepithelial wound healing. Honey toxicity to keratinocytes and fibroblasts is relatively low. The immunomodulating effect could improve the antimicrobial activity of honey. At a moderate amount of inflammatory mediators or stimulators from keratinocytes, honey enhances inflammatory cytokines and MMP-9. Furthermore, during infection and inflammation in wounds, honey inhibits the release of inflammatory cytokines and MMP-9[34)].

Antimicrobial activity

When the immune response cannot clear up the infection, such as in burns, antimicrobial therapy should be considered[25)]. The antimicrobial effect of honey is associated with the high sugar, low pH, H_2O_2, and osmotic effect, although honey's benefits are based on the variety and concentration of administration[6,35,36)]. Honey has been shown to have broad-spectrum anti-infectious action against Gram-positive and -negative bacteria, be it aerobic or anaerobic. Several previous *in vitro* studies have shown that honey could inhibit bacterial pathogen development[6,37)]. Increasing interest in using honey for infected wounds is reinforced by antibiotic resistance development because honey has proved effective against antibiotic-resistant bacteria. Unlike antibiotics, bacteria do not develop resistance to honey[5,8)].

Bacterial growth and the shape of bacterial cells depend on the integrity of the cell walls. A study revealed that honey could inhibit the synthesis of cell walls from inducing structural changes in them. The mechanism of honey is similar to that of ampicillin, which can alter the shape of cells and the *Escherichia coli* lipopolysaccharide membrane. Therefore, honey is an appropriate substance to be an antibacterial agent[38)].

Antiinflammatory activity

Inflammation is a biological reaction to self-protection to remove foreign microorganisms from infection and initiate a healing phase. Increased free radical concentration could damage and decompose lipids, proteins, and nucleic acids during the inflammatory stages of wound healing, all of which are important for cell function. With its phenol content, honey reduces the effects of free radicals, preventing further tissue necrosis. Reactive oxygen species (ROS) produced during an inflammatory phase could stimulate fibroblast activity. Collagen fibers from fibroblasts forming scar tissue, and a persistent inflammatory reaction may induce hypergranulation and fibrosis[34)].

Consequent to using honey, the inflammatory phase reduced and minimized or prevented hypertrophic scarring. The underlying mechanism is the nuclear factor kappa B (NF-κB) pathway inhibited by honey. It converts NF-κB into the nucleus and minimizes inflammatory mediators, including TNF-α and COX-2[34,39)].

Antioxidant activity

ROS mediates the cytotoxicity induced by TNF-α during the inflammation process. Neutrophils and macrophages generate higher levels of ROS during chronic wounds to fight bacteria. Tissues with long-term exposure to ROS could damage the cells and delay wound healing. Consequently, antioxidants are required to eliminate ROS, and they are naturally found in honey[34]. The flavonoids in honey could also scavenge ROS, alkyl peroxide, hydroxyl, peroxyl, and superoxide radicals. These substances resist reactive nitrogen species (RNS) tissues, including peroxynitrite and nitric oxide (NO)[30,31].

Burn and wound healing stimulation

Several studies have shown honey's efficacy in treating acute (burns and lacerations) and chronic wounds (venous leg ulcers and pressure ulcers)[28,34,40]. For the wound to heal, it must go through 3 main repair processes. The process begins with inflammation, proliferation, and remodeling. Honey stimulates the development of inflammatory mediators from monocytes in the inflammatory process, including IL-1β, IL-6, TNF-α, and NO, making fibroblasts synthesize collagen. Honey also has phenolic components that serve as an inhibitor of inflammatory processes. In altering the inflammatory stage, where inflammation is active but regulated, honey prevents inflammation becomes excessive. Furthermore, honey will decontaminate debris and bacteria from wounds by enhancing phagocytosis during the inflammatory process[8,41,42].

Honey could also indirectly provide nutrients to wounds through the osmotic lymph flow and directly through the intake of amino acids, carbohydrates, minerals, and vitamins, effectively metabolized. The epithelial cells need carbohydrate reserves for energy migration on the wound surface to restore the epithelial sheaths, and glucose could provide glucose for leukocytes, epithelial cells, and glycolysis processes[5,8]. The proliferation process involves angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction. During this process, honey enhances the oxygen supply to the angiogenesis needed by the wounds[8,43].

Honey increases wound contraction by enhancing myofibroblast, fibroblast, and collagen accumulation. Such a mechanism also encourages reepithelialization. High osmotic pressure keeps the edges of the wound attached[44]. Honey has low levels of H_2O_2 and induces the growth and development of new capillaries, fibroblasts, and epithelial cells in the wound tissue. On the other side, with its antioxidant properties, phenol helps protect cells from toxic effects[44,45]. Reepithelialization is a crucial phase that causes keratinocyte proliferation and migration on the skin's surface. Honey also contains Fe, Co, Mn, Cu, Mg, and Zn, promoting the proliferation of keratinocytes by controlling integrin expression throughout reepithelialization. MMP and plasmin molecules produced by immature keratinocytes could differentiate and facilitate keratinocytes' migration from the basement membrane. Collagen is restructured and rebuilt throughout the tension line. After that, apoptosis will dispose of unnecessary cells. Honey could reduce burn scarring and scar contracture in patients and improve skin regeneration[4,7,8].

Mechanisms of action of snakehead fish skin in burn and wound healing

Healing properties of snakehead fish skin

A previous study reported that snakehead fish skin's protein content increases, corresponding to body weight[11]. The protein was also rich in albumin, which plays a role in accelerating wound healing[9,46]. The essential amino acids were available in snakehead fish skin (arginine, phenylalanine, valine, tryptophan, lysine, isoleucine, leucine, methionine, threonine, and histidine), and many non-essential amino acids (cysteine, tyrosine, aspartate, alanine, glutamate, proline, serine, and glycine). Neither glycine nor proline is the maximum level of amino acids found in the snakehead fish with medium-, large-, and small-sized snakehead fish[11]. Glycine with arachidonic acid plays a role in prostaglandin precursors[46]. Meanwhile, proline helps wound healing, antioxidant reaction, and immune response, and arginine also helps hydroxyproline production form connective tissue[11].

Studies in rats and humans have shown that arginine supplementation has an accelerated effect on wound healing. This is because of increased collagen deposition and mitogenesis of peripheral blood lymphocytes[47]. Another study also reported that the group receiving arginine in healing stage II-IV ulcers experienced a twofold increase[48]. This finding proves that arginine synergizes with other amino acids to generate new tissue in wound healing[11].

Meanwhile, the minerals in snakehead fish skin include Na, Mg, S, Cl, K, P, Ca, and Zn[11,46]. Another collagen content is already identified as an active ingredient for accelerating wound healing recovery[11,49]. This is supported by the similarity of type 1 collagen in snakehead fish and humans. Another component in snakehead fish skin is hydroxyproline, which exists only in the connective tissue containing collagen and elastin. Hydroxyproline supplementation for the feed of cultured snakehead fish increases the amount of collagen in the skin tissue[11]. An experiment with pigs as a model given a collagen gel as a treatment for excised wounds has proved that collagen gel induces vascular endothelial growth factor (VEGF) and signal transduction of cells for wound healing[50].

Mechanism of snakehead fish skin in wound healing

Wound healing works well if the influencing factors could be controlled. Local conditions around the wound, including infection, could prolong the wound-healing process. Infection of the burn occurs more quickly because the skin loses integrity[16]. In patients with contaminated wounds, bacteria like *Staphylococcus aureus* and *Pseudomonas aeruginosa* are commonly encountered[51]. According to research by the *Center for Aquaculture Research and Extension* (CARE), antimicrobial properties are identified in the snakehead fish skin. They show a broad spectrum against *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, and *Vibrio anguillarum*[52]. Besides the antimicrobial properties, there are antioxidant compounds from amino acids and fatty acids in snakehead fish's skin[53]. The compound is expected to reduce infection and oxidative stress that could prolong the wound-healing process[52,54].

Another factor contributing to wound healing is the immune system. These factors have a vital role in the inflammatory process. The nutritional intake of burn patients should be examined to produce an adequate immune response. The state after the burn where the loss of tissue proteins causes an optimal immune response. Such circumstances could be minimized with snakehead fish components, such as albumin, glycine, and Zn[46].

Zn is essential in the wound healing process. Zn deficiency results in reduced B cells, phagocytosis, cytokine production, and impaired microbial cell destruction. Also, protein in snakehead fish, albumin, and glycine will bind Zn from the outside to limit free radicals and help regulate lymphocytes. Zn in snakehead fish extract also likely becomes the critical factor in children's increased appetite. Other nutrients and vitamins in snakehead fish could trigger endothelial progenitor cells formation and accelerate wound healing[46]. Also, wound healing requires protein as the basis for collagen synthesis. Meanwhile, collagen repairs injured parts of the body and provided normal structural strength to tissues. Albumin and glycine protein in Snakehead fish could be a wound-healing agent because as an antioxidant agent and stimulator of fibroblast cell proliferation, increasing collagen production[44,55].

The potential of gels with honey and snakehead fish skin substituents for burns

The rationale behind gel use

Honey is challenging to apply directly to burns because the properties could melt at high skin temperatures, and the treatment takes a long period to achieve therapeutic concentrations. This limitation could be overcome by formulating honey into hydrogels[56]. The advantages of honey in a hydrogel formulation include good transparency, the ability to absorb exudate, and an acidic pH that provides an ideal environment for wound healing[57]. Also, a study on gel formulations using snakehead fish extract reported that wound healing could accelerate because of an addition of neutrophil and macrophage cells[58].

A previous study reported that Manuka honey-based hydrogel had become a solution since it has proven effective in preventing bacterial infection. The bacteria that inhibit Manuka honey-based hydrogel include *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*[59]. Also, there are no cytotoxic effects in Manuka honey-based hydrogel applied to human mesenchymal stem cells. The evidence by 20% of honey hydrogels causes almost 100% inhibition, while non-honey hydrogels cause about 20% inhibition of both types of bacteria[28]. A previous study reported that Manuka honey-based hydrogel effectively prevents bacteria infection, including *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, without causing cytotoxic effects[59].

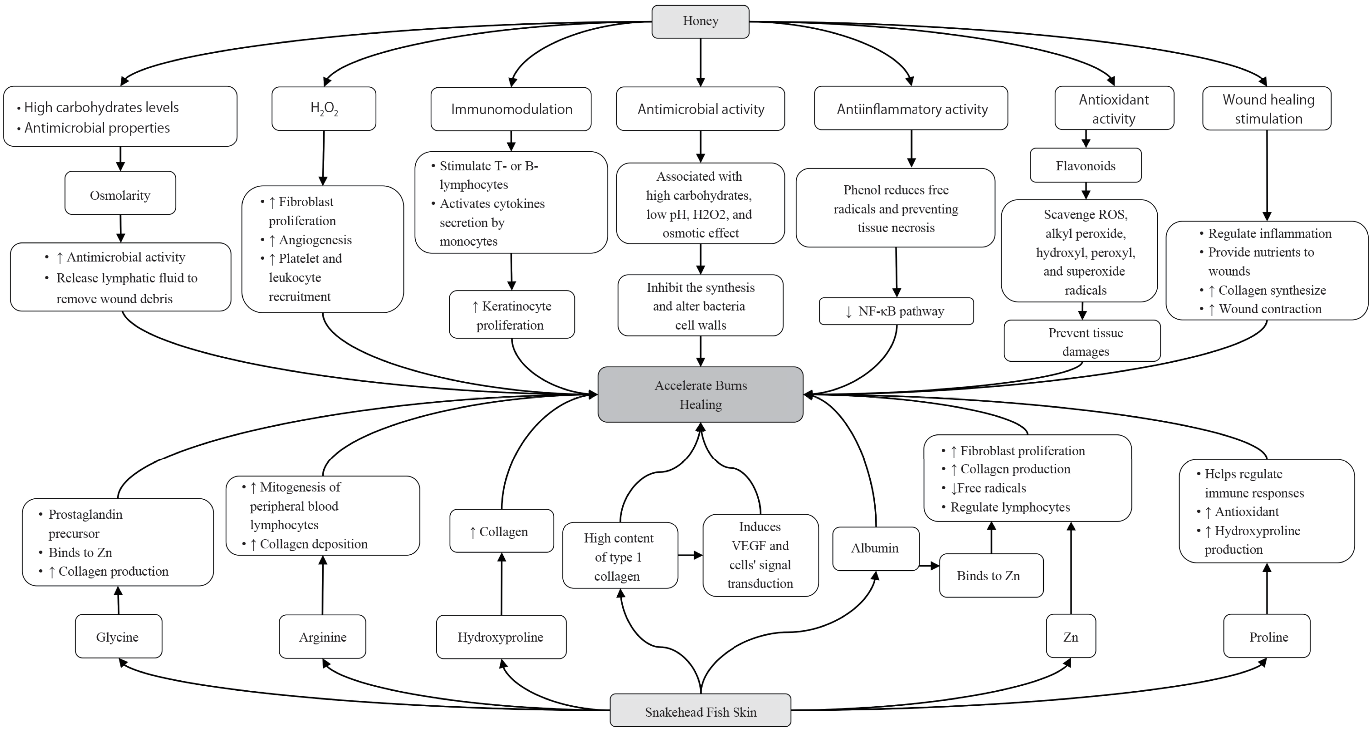

Figure 1: Summary of the potential synergistic effects of honey and snakehead fish skin. ↑: Increase, ↓: Decrease, H_2O_2: Hydrogen peroxide, NF-κB: Nuclear factor kappa B, ROS: Reactive oxygen species, VEGF: vascular endothelial growth factor

The potential effects of honey and snakehead fish skin-based hydrogel

Using honey-based gel is effective in facilitating healing from burn injuries. This is proved by a study in which the rat's wounds treated using a honey-based hydrogel had a significantly increased wound contraction rate than the control group within 21 days after burns. Also, histopathological evaluation has proved that honey-based hydrogels reduce the inflammatory response and increase reepithelialization[60)]. Another study reported that a snakehead fish-based gel formulation successfully accelerates the healing of incised wounds by increasing the number of fibroblasts and improving white rats collagen density[58)]. Thus, combining honey and snakehead fish skin seems to have a promising effect (Figure 1).

CONCLUSION

The combination of honey and snakehead fish skin as a hydrogel preparation elucidated above seems promising for a synergistic and beneficial effect for healing burns. It is because honey contains antimicrobial, antiinflammatory, antioxidant, and H_2O_2 properties, high osmolarity, and the ability to modulate the immune system and stimulate wound healing. Also, snakehead fish skin's healing properties, rich in protein, minerals, and collagen, will accelerate the wound healing process. Therefore, this review is expected to become an essential reference for further research.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL STATEMENT

No ethical approval was required as this study did not involve human participants or laboratory animals.

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