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Effect of chicken bile application on scar healing process: literature review

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ABSTRACT

The type of scars varies from mild fine-line scars to abnormal scars, and treatment will differ according to its type, location, symptoms, and severity. Scars greatly impact human life physically, aesthetically, psychologically, and socially, making choosing the right treatment very important. Treatment for scars can be done conventionally in healthcare facilities and traditionally. Chinese traditional medicine has been known to affect scar treatment majorly. Wound healing is composed of three initial stages, such as inflammatory, proliferative, and remodeling stage. Chicken bile is known to have a low but strong bilirubin level with little biliverdin. These agents can serve as antipyretic, antioxidant, anti-inflammatory, and anti-atherogenic, aiding wound healing. Bile also supports protein metabolism, fat metabolism, energy production, and glycogen synthesis. Most importantly, bile contains matrix metalloproteinases (MMPs) that degrade type IV collagen, which have an important role in the wound reepithelization process, altering wound matrix, enabling the cell to migrate, and tissue remodeling. Thus, it is certain that MMPs are essential in wound healing.

Keywords: chicken bile, chicken bile effect, wounds, the wound healing process.

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INTRODUCTION

Various types of scars can affect the skin, ranging from mild fine-line scars to abnormal scars. Examples of these are widespread scars, atrophic scars, hypertrophic scars, keloid scars, and scar contractures. In treatment, many aspects have to be considered. Scar type, site, symptoms, severity of functional impairment, and social stigma will determine this decision. The type of scar is the most significant factor among others. Thus one of the reasons why for each scar, healing treatment and duration will differ.¹ In general, there are three healing stages: the inflammatory stage, the proliferative stage, and the remodeling stage. The inflammatory stage will start immediately and stop a few days later. Disinfection of the wound will happen in this process, thus making the wound swollen and pink. Beginning in the third or fourth week, fibroblasts will produce collagen at the injury site, creating new capillaries to aid the healing process, making the wound thicker and red. The scar will turn white and barely noticeable at the remodeling stage, which happens until a

year afterward. Unfortunately, keloid scars are much different compared to others. Fibroblast continued to fill the wound, potentially leading to the piling up of a large mound on the scar surface, making it grow.²

Each scar can heal, although, for each type, this process may vary. Normal fine-line scars usually heal after two years, but visible marks remain. Hypertrophic and keloid scars can grow six months after the wound has healed. Anthropic scars and contractures shrink the skin, leading to longer healing times.³ Since skin is one of the largest and outermost organs that wraps the body, it is vulnerable to many traumas, making epidemiology quite worrisome. Each year 100 million patients acquire scars. For instance, mild fine line scars have an epidemiology of 55 million yearly after operations,¹ hypertrophic and atrophic scarring after burn injuries are 8% - 90.8%, and contractures can happen 38% - 54% of the time.² Keloid scars are estimated to compose eleven million from 100 million scars that develop.¹⁴

All of these scars happen often and need a longer healing time. High frequency and longer natural healing time can greatly

impact human life physically, aesthetically, psychologically, and socially. Physical consequences include scar contractures, aesthetically unpleasant skin, severe itching, and tenderness. Psychological effects such as anxiety, depression, post-traumatic stress reactions, and loss of self-esteem can also arise. Socially, it can cause stigmatization.¹⁵

Incidents and burdens because of wounds have become a major health concern and even more so in the recent pandemic because healthcare facilities have become limited. With these challenges in using conventional treatment, traditional medicines are selected to provide better care for patients.⁶

The use of chicken bile in wound healing stems from Chinese traditional medicine based on the knowledge that the final stage of wound healing involves the organization, degradation, and re-synthesis of the extracellular matrix. In this stage, the wound will undergo a process that aims to restore the previous tissue structure; therefore, a collagen degradation process is needed, formed during the proliferation phase by the body's cells. In addition to being degraded

by cells, some substances, namely the matrix metalloproteinase enzyme, play a role. Matrix metalloproteinases, or MMPs, are enzymes that play a role in protein degradation, including collagen found in the extracellular matrix.⁷ Chicken bile contains MMPs, enzymes that break down extracellular matrix proteins, such as collagen and proteoglycans. Matrix metalloproteinases can also digest collagen, which is resistant to conventional gastric proteases. Bile is useful in poultry as it helps emulsify and digest fats in the intestines.⁸ This literature review aims to increase the reader's understanding of the use of components found in chicken bile in aiding wound healing to give higher chances of using it as another way of wound treatment.

WOUND HEALING PROCESS

Wound healing is a complex process of the human body when dealing with tissue damage. There are three stages of the wound healing process. The first is the inflammatory stage.⁷ This initial stage starts at the onset of the injury. Which objective is to stop further damage, whereas the human body will close the site of injury with several mechanisms such as hemostasis which consists of a coagulation process and vasoconstriction pathway to stop further bleeding, activate chemotaxis response to start inflammatory cells migration and send leucocyte to the injury area which leads to the activation of immune response and pro-inflammatory cytokines. The duration of this stage ranges between 24 hours to two weeks in normal conditions.^{6,11}

The second stage of wound healing is the proliferative stage, which starts in the first 48 hours after the onset of the injury. In this stage, there are three main processes, reepithelization, angiogenesis, and fibroplasia, whose objectives are to close the wound and lower the injury.⁷ Reepithelization is a process of forming epithelium tissue and its surrounding components. This will restore the outer part of the injury, acting as a protective layer to prevent the body from encountering another injury.^{8,10} Angiogenesis is a process of making new vascularization to supply oxygen and nutrients to the tissue. This process is promoted by VEGF or

vascular endothelial growth factor, which is released by the macrophage in the previous stage of wound healing.¹²

The last stage is the remodeling stage. This stage is the most important process for forming a scar. In this stage, the scarring process happens, and collagen builds up in the wound area, ranging from weeks to years, depending on the genetics and the patient's condition.⁷ With the completion of the inflammatory response, the aim of this stage is no longer to make initial protection but rather to form a stronger tissue by changing the composition and arrangement of the cellular matrix. Type I collagen is produced in this process, and some other structures are degraded. For instance, fibronectin and hyaluronic acid degradation by plasma metalloproteinase enzyme.^{11,13}

Chicken Bile

Bile is produced in the liver. It comprises a complex mixture of bile acids such as cholesterol derivatives, heme-derived pigments, mucus, enzymes, and protein breakdown products. It also plays an important role in emulsifying and digesting fat in the intestines.⁸ A study conducted by Wang and Carey, 2014 stated that the gallbladder with concentrated hydrophobic bile acids has a strong mechanism of action similar to detergents and can kill pathogens through cell membranes and cell wall disruption. Bile in traditional Chinese medicine has a low but strong bilirubin level and rarely contains biliverdin. These agents have antipyretic, antioxidant, anti-inflammatory, and anti-atherogenic characteristics, which meet the requirement to cover wounds, burns, or ulcers.¹⁴

Components of Chicken Bile

Chicken bile possesses a variety of active ingredients, with each important performing function. Proteases and peptidases will play a role in producing free amino acids in protein metabolism. Meanwhile, in the metabolism of fats, a component of bile called choline will assist fat deposition and energy production. Bile also supports the synthesis of glycogen and the conversion of lipids into fat in carbohydrate metabolism.¹¹ A research by Packialakshmi et al. showed that on top

of the previously mentioned components, chicken bile is rich in endopeptidases called matrix metalloproteinases (MMPs). They are enzymes that cleave extracellular matrix proteins such as collagen and proteoglycans. Matrix metalloproteinases (MMPs) in bile aid the digestion of native collagen, which is resistant to conventional gastric proteases. The matrix metalloproteinases protein bands in avian biles belong to the type IV collagenase group, MMP2 or gelatinase A. The level of MMP2 in avian bile may be modulated by dietary factors such as gelatin-supplemented diets that can increase the amount of MMP in the bile. However, the food given to the animals can modify the adaptive regulation of their functions.⁸

Characteristics and Functions of Active Components in Chicken Bile

Matrix metalloproteinases (MMPs) in chicken bile are MMP2 or type IV collagenases that degrade type IV collagen. This type of collagen is found in human organs such as the skin, specifically in the basement membrane, in which an extracellular matrix composes the bottom of skin epithelial cells.¹² Matrix metalloproteinases (MMPs) are shown to be present in both acute and chronic wounds. With their inhibitors, they have a crucial role in regulating extracellular matrix degradation and deposition, which is important for the wound reepithelization process.¹³

During wound repair, studies show increased gene expression of MMP-2, MMP-3, MMP-9, MMP-11, MMP-12, MMP-13, and MMP-14.¹⁴ They are involved through the stages of wound healing by altering the wound matrix, enabling the cell to migrate and tissue remodeling. The locations of wound healing are controlled by cross-talk between various components, including extracellular matrix, growth factors, integrins, and MMPs. The migration of cells in ECM, remodeling, and degradation of ECM by MMPs are key wound repair mechanisms.¹³ On the first day after the injury, MMPs are produced by inflammatory cells to help cleanse the wound from impaired ECM and tissue. MMPs also assist the formation of granulation tissue by acting on the

basement membranes of arterioles which will help endothelial cells to migrate from new vessels to contact the wound bed.¹⁴

The migration of keratinocytes demands the basal epidermal keratinocytes hemidesmosomes to dissolve, impeding their contact with the basement membrane and permitting migration through the wound matrix.¹³ The timed expression and activation of MMPs in response to wounding are vital for successful wound healing.¹³ Apart from MMPs' functions on collagen and wound repair process, there is also the probability of their effect on gastrointestinal matters, such as their capability to activate growth factors, antimicrobial proteins, receptor proteins, and other proteases other than MMPs that need to be explored more in the matters of digestive physiology.⁸

In short, it can be concluded that MMPs, as a component of chicken bile, one of the crucial factors needed in wound healing because of their functions in cleaning the wound and altering the wound matrix to enable cell migration and tissue remodeling, which will support wound healing process.^{13,14}

Application of Chicken Bile in Wound Healing

Matrix metalloproteinase (MMPs) can be applied topically to the skin as a type of endopeptidase. However, its form of application is still debated and rarely discussed. However, to maximize the use of MMPs, an ideal environment is necessary to ensure a good wound-healing process. In wound healing, factors such as good debridement are needed to remove unhealthy tissues and cells in MMPs production, appropriate wound dressings which can inhibit bacteria proteases such as superabsorbent polymers to bind and decrease the counterproductive activity of MMPs and other types of wound dressings which have high ionic charges to decrease MMPs overproduction.¹⁵

In addition, other substances can support wound healing, such as collagen and tissue-based dressing that can replace wound healing modulators as a collagen attack target, thus, further facilitating wound healing, topical drugs, antibiotics, and dressings as a functional component in regulating MMPs, and negative pressure wound therapy in aiding drainage and suppressing overproduction of MMPs.¹⁵

CONCLUSION

The wound healing process has several phases that must be passed. One of them is the remodeling process. In this process, wound healing requires metalloproteinase enzymes. Research shows that chicken bile has many of these components needed in the wound healing process. However, these components can affect gastrointestinal problems, so further clinical trials related to digestive physiology are required.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest in this publication.

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AUTHORS CONTRIBUTIONS

Author CFL is the main author in conducting the research method. Authors MHI, PJJ, and MAT participated in constructing the research manuscript. Author LMMS as the supervisor in the manuscript progress.

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