

Mechanism of Xiangpi Shengji Ointment to Promote Wound Healing

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Abstract: *The wound is a common surgical disease characterized by skin and tissue defects or limited function. Wound healing is a prerequisite for the recovery of the body's function after trauma. If the wound is not treated in time, infection will occur. If the inflammatory response is excessive, it will affect the speed and quality of healing. In recent years, there have been more and more clinical studies on Xiangpi Shengji Ointment in promoting wound healing, showing great clinical value. As a common medicine in the field of traditional Chinese medicine surgery, Elephant Skin Skin Cream has the effect of removing pain and muscle, reducing inflammation and long skin. At present, clinical Xiangpi Shengji Ointment is used to treat postoperative wounds, pressure ulcers and diabetic foot ulcers after anal fistula. This paper will discuss the composition and efficacy of Xiangpi Shengji Ointment, the application of the method of simmering pus and meat, and the influence of the active ingredients of Xiangpi Shengji Ointment on the expression of inflammatory factors, growth factors and signaling pathways, so as to effectively promote the healing of wounds. The purpose is to analyze and explain the mechanism of the role of Xiangpi Shengji Ointment in wound treatment in order to promote its promotion in clinical application.*

Keywords: Simmering pus and growing meat, Wound, Xiangpi Shengji Ointment, Mechanism of action.

1. Introduction

A wound refers to damage caused by normal skin or tissue under the action of external injury factors or factors in the body, often accompanied by the destruction of skin integrity and loss of normal tissue. Wres can be divided into acute injuries caused by accidental injury, iatrogenic injury or biogenic injury, and chronic injuries such as pressure ulcers, ulcers or diabetic foot. The vulnerability and difficulty of the wound not only causes patients to suffer a double physical and mental blow and loses their confidence in life, but also makes families sleepy due to illness due to expensive treatment costs. With the rapid increase of China's aging population, the burden of chronic diseases has shifted, and the prevalence of complex and chronic lesions has also increased year by year. Epidemiological research shows that chronic wound patients in China account for 1.7% of hospitalized patients, and more than 50% of patients face multiple operations but have poor results [1]. Therefore, how to effectively control the development of wound diseases and improve the quality of wound healing in patients has become one of the key issues in clinical research. In recent years, due to the unique advantages of high safety, few side effects, accurate curative effect and long-term external use in the treatment of wound healing of traditional Chinese medicine, more patients are inclined to choose traditional Chinese medicine for wound healing treatment, and the traditional Chinese medicine "elephant skin ointment" commonly used in the field of traditional Chinese medicine surgery has attracted more attention. The study found that [2], Xiangpi Shengji Ointment combined with the theory of "simmering pus and long meat" can regulate the body's immune system, so that the local microvessels of the wound produce exudate rich in immune active factors, effectively restore the function of wound tissue cells, and then achieve the effect of anti-infection and accelerated wound healing.

2. Xiangpi Shengji Ointment

Xiangpi Shengji Ointment is composed of elephant skin, gypsum, blood residual charcoal, calamine, Angelica, native yellow, tortoise shell, beeswax and other drugs. It is derived from the "Outline of Selection" compiled by Zhang Shanlei (1872-1934), a physician in the early years of the Republic of China. It is a classic prescription commonly used Its main drug is elephant skin, which tastes, is sweet, salty, and warm. It is good at making muscle abrous and sores to stop bleeding. It is a flesh-and-blood affectionate product. The "Yi Xue Ru Men" written by the Ming Dynasty contains: elephant skin can be decoated, which can decay and produce new, and can accelerate the convergence of sores. It can be seen that the main effects of elephant skin [3]. Raw gypsum is a commonly used medicine in surgery and has the effect of muscular astringent sores. Blood residual charcoal has the effect of muscular astringent sore, stopping bleeding and removing blood stasis. The "Yi Xue Zhong Zhong Can Xi Lu" said: "For those with residual blood, if they do not calcinate, their quality will not melt, so they must be calcined into charcoal and then put into medicine. Its properties remove blood stasis and produce new blood like Sanqi, and calamine is a mineral drug." "Ben Cao Hui Yan" contains: "Huscalane can grow muscles, harvest dampness, and adverage sores [4]." The four drugs of elephant skin, raw gypsum, blood residual charcoal and calamine are matched to play the work of muscle advergence sores, so that the stubborn sores on the surface are purulent, water and hot poison, wet and poisonous, and the blood blood is smooth and fresh. Angelica has the function of replenishing blood and blood, and has the effect of stopping bleeding. It clears the heat and cools the blood, nourishes yin and nourishes fluid, and is used to treat the syndrome of yin deficiency and internal heat. The turtle board nourishes yin and latent yang, nourishes the kidney and strengthens bones, nourishes the blood and calms the mind. Beeswax is an excitant, which can nourish damaged skin on the outside, intercept heat on the inside, nourish blood and body fluid. Looking at the whole prescription of warm meat and simmering pus, growing muscles and skin, activating blood circulation, nourishing blood and remove blood stasis, it not

only excludes the standard of the lesion, but also takes into account its root, so it has a good effect in treating wound healing.

3. The Mechanism of Combining the Theory of "Simmering Pus and Growing Meat"

The wound belongs to the category of ulcer, ulcer and sore in traditional Chinese medicine. Traditional Chinese medicine believes that the pathogenesis of sores is caused by qi and blood coagulation caused by toxic internal invasion, evil heat, blood burning and other factors. Therefore, the patient has symptoms of poor qi and blood circulation, poor new blood, lack of nutrition in the wound, and unable to produce granulation tissue. As a special treatment of traditional Chinese medicine surgery, it is often used to treat some wounds with large, chronic and difficult to heal, such as pressure ulcers, diabetic feet, surgery-related non-healing wounds, open infections and burns and other surgical "sores" diseases [5]. Therefore, traditional Chinese medicine often uses the theory of "simmering purulent and long flesh" combined with plaster to promote blood circulation and remove blood, remove blood circulation, stop bleeding, relieve pain, and muscle growth to treat chronic reversable wound, and often receives better results. For example, Cao Wenzhong et al. [6] used Xiangpi Shengji Ointment according to the method of simmering purulent flesh to heal the wound, accelerate local blood circulation, improve the nutrition of surrounding tissues, promote the rapid shedding of necrotic tissue, accelerate the rapid growth of cell tissue, and thus accelerate wound healing. According to the theory of "simmering pus and growing meat", Lu Xuya and others found that the best frequency of dressing is once every two days, and the wound healing is the fastest. The above studies show that the obvious advantages of Xiangpi Shengji Ointment combined with simmering pus and long meat in the treatment of wound healing provide a theoretical basis for further exploring the mechanism of Xiangpi Shengji Ointment to promote wound healing.

Xiangpi Shengji Ointment combined with simmering pus and long meat can better play the medicinal effect and promote wound healing. Among them, the "puscess" of simmering pus meat is the pus simmered out of traditional Chinese medicine, reflecting the interaction between external Chinese medicine and the wound, that is, with the continuous action of external Chinese medicine and the increase of wound exudate, the purulent composition can be dynamically changed, thus forming a "purative" microenvironment suitable for wound growth [8]. Therefore, some scholars believe that the essence of "simmering pus and growing meat" is to maintain the internal environmental self-stabilization state of neonatal granulation tissue and bacteria under the condition of infection through external traditional Chinese medicine [9]. Wang Hongxu's "Wai Ke Quan Sheng Ji" proposed: "The transformation of heat poison must be caused by pus, the pus must come from qi and blood, and the transformation of qi and blood must be caused by warmth. How can it be cool?" "The Yi Zing Jinjian" said: "The corrupt, the bad meat, and the books say: If you don't rot, you won't be new." Externally, Xiangpi Shengji Ointment warms and moisturizes the wound, so that the wound exudes a clean and odorless "pus" and nourishes the wound with "pus", which has the effect of

warming meat and simmering pus and growing skin. In the composition of plaster, the combination of the four drugs of elephant skin, raw gypsum, blood residual charcoal and furnace gan stone can produce the effects of dredging meridians, clearing heat and detoxifying, antiseptic and muscle growth, hydrating and swelling, etc., and achieve the effect of simmering pus and growing flesh. If you simmer, it will be warm; if you will have pus, you will have qi and blood. The essence of pus is the biochemical of qi and blood. Angelica function is tonic and benefit qi and blood, and it is also a warm medicine. If it is warm, it will make local qi and blood smooth, and then increase the secretion of the wound to achieve the purpose of moistening the wound. Shengdihuang and tortoise shell have the function of nourishing yin and generating saliva. The wound secretion is the lost saliva to maintain the balance of the body's saliva. As a matrix, beeswax promotes drug penetration, protects granulation tissue, and eventually produces the effect of removing rotting muscles and simmering pus. In addition, modern pharmacology shows that [10-12] raw gypsum, blood residual carbon and calamine all have anti-inflammatory and sterilization effects, so that the pus simmered out of traditional Chinese medicine will not induce inflammation, achieve the internal environmental self-stable state of symbiosis between newborn granulation tissue and bacteria, and promote wound healing.

4. Mechanism of Wound Healing

According to relevant literature [13], the mechanism of wound healing is mainly related to inflammatory factors, growth factors and signaling pathways. (1) Inflammatory factors: After skin damage, inflammatory factors can activate and chemotify a large number of immune cells, complements and antibodies to the locally damaged wound, inhibit or remove bacteria, activate the body's immune response to trauma, and promote the healing of skin wound tissue. It is an indispensable key link for wound repair [14]. Tumor necrosis factor- α (TNF- α), interleukin (IL)-6 and IL-8 are important inflammatory factors, which play an important role in the repair of skin wound tissue. TNF- α can promote wound healing by inducing the expression of a variety of inflammatory factors, regulating immune function and promoting the migration and proliferation of keratinocytes [15]. In the process of wound healing, IL-6 plays a role in promoting wound tissue healing by activating the body's defense mechanism, participating in the body's defense against infection, inflammatory response and immune response, and limiting further damage to the body [16]. (2) Growth factor: In the process of skin wound healing, growth factor has biological effects such as inducing and stimulating the proliferation of damaged tissue cells, extracellular matrix protein synthesis, and maintaining cell survival. It is an extremely important protein substance to promote the healing of damaged wounds [17]. Growth factors mainly include vascular endothelial growth factor (VEGF), alkaline fibroblast growth factor (bFGF), transformation growth factor β (TGF- β), insulin-like growth factor 1 (IGF-1), etc. [18]. VEGF is an important factor that promotes angiogenesis. It can stimulate new angiogenesis and growth, restore damaged vascular networks, improve tissue blood supply, and promote wound healing [19]. bFGF can promote the proliferation and migration of wound fibroblasts, and induce vascular

endothelial cell proliferation and angiogenesis. It is a multi-functional growth factor [20]. TGF- β is one of the cytokines closely related to wound healing [21]. It can chemochemical and fibroblastst the concentration of inflammatory cells into wounds, promote granulation tissue growth and epidermis formation, and is a multi-functional cytokine that can regulate wound repair [22-24]. IGF-1 can induce the proliferation and differentiation of fibroblasts at the appropriate concentration [25], thus promoting wound healing. (3) Signaling pathway: The signaling pathway plays a central role in wound healing, affecting the healing speed and quality of the wound by regulating cell activity and participating in the inflammation and repair process. For example, the PI3K/AKT pathway promotes cell repair by regulating biological functions such as cell migration, gene expression and material metabolism in the process of cell damage healing [26].

In summary, in the long and complex process of wound repair, related inflammatory factors such as TNF- α , IL-6 and IL-8 can regulate the body's immune function and activate the defense mechanism. VEGF, bFGF and other related growth factors can promote the proliferation and differentiation of various tissue cells such as epidermal cells, vascular glial cells and smooth muscle cells, and promote the production of new blood vessels and the growth of granulation tissue. PI3K/AKT and other pathways can connect intracellular effects, regulate biological functions such as cell migration, gene expression and substance metabolism, and then participate in the healing of skin wound tissue.

5. Mechanism of Action of Xiangpi Shengji Ointment

5.1 Regulate the Expression of Inflammatory Factors

Xiangpi Shengji Ointment can adjust the expression of a variety of inflammatory factors, such as IL-6, IL-8 and TNF- α , to promote wound healing. IL-6, IL-8 and TNF- α are all cytokines with extensive biological activities and play an important role in the body's immune response, metabolic regulation and inflammatory response. When the wound has an inflammatory reaction, the serum IL-6 level will increase, reflecting the body's response to inflammation, which is an important indicator of the degree of inflammation of the sensitive reaction [27]. Its high expression is related to the intensification of the inflammatory response and delayed recovery of tissue loss. In the inflammatory reaction, IL-8 can chemotide T lymphocytes, neutrophils and basophils to reach the focal site, forming a local inflammatory reaction to achieve the purpose of sterilization and reducing cell damage. It is an indicator of early inflammation [28]. IL-8 and TNF- α are important inflammatory factors for wound repair [29]. Overexpression of IL-8 and TNF- α can affect wound healing and recovery function. It has been found that Zeng Tingting and others [30] have the effect of Xiangpi Shengji Ointment on the expression of IL-8 and TNF-alpha proteins in model rat wounds after anal fistula surgery. Epidermal muscle ointment can significantly reduce the expression of IL-8 and TNF- α proteins, reduce wound edema, significantly improve the wound healing rate, and promote wound healing. Zhang Xinyan and others [31] suggest that Xiangpi Shengji Ointment can also reduce the inflammatory response of local

wounds by reducing the expression level of IL-6 and TNF- α , and promote the healing of model rat wounds after anal fistula surgery. Therefore, Xiangpi Shengji cream can reduce the wound inflammatory response and promote wound healing by inhibiting the expression of inflammatory factors such as IL-6, IL-8 and TNF- α .

5.2 Regulate the Expression of Growth Factor

At present, the adjustable growth factors in the treatment of wound healing are mainly vascular endothelial growth factor (VEGF), alkaline fibroblast growth factor (bFGF) and transformation growth factor β (TGF- β). Vascular endothelial growth factor (VEGF) is a highly specific cytokine that promotes the growth of vascular endothelium. It can promote the formation of newborn capillaries on wounds, provide necessary blood and nutrients for tissue growth, and plays an important role in tissue healing [32-33]. Alkaline fibroblast growth factor (bFGF) is a capillary proliferation stimulant. Its biological functions mainly include promoting the wandering of endothelial cells and repairing damaged endothelial cells, the proliferation of smooth muscle cells, promoting angiogenesis, promoting trauma healing and tissue repair, etc. [34]. Zhang Xinyan et al. [31] repaired the postoperative wound of rat anal fistula with Xiangpi Shengji cream group, model group and fake surgery group respectively. It was found that after treatment, the water level of VEGF and bFGF of rat wound tissue in each group was significantly increased, while the level of VEGF and bFGF of rat wound tissue in the Xiangpi Shengji Ointment group was significantly higher than that of the model group, suggesting that Xiangpi Shengji cream could promote the healing of the wound VEGF and bFGF wound by promoting the healing of the wound. Its main mechanism may be related to the fact that the skin cream can reduce the level of inflammatory factors in rats and promote the expression of VEGF and bFGF. TGF- β cytokine is currently recognized as one of the cytokines closely related to trauma healing [35]. Its main function is to gather chemofibroblasts and inflammatory cells to the wound, induce granulation tissue growth and epidermal formation. It is a kind of multifunctional cytokine that plays an important regulatory role in wound repair. Zhang Yuejuan and others [36] repaired the rat pressure ulcer wound with different drugs. It was found that the expression of TGF- β on the wound treated by Xiangpi Shengji cream was significantly higher than that of other groups. It was believed that Xiangpi Shengji cream could increase the expression of TGF- β in the newborn granulation tissue, thus accelerating wound healing. To sum up, Xiangpi Shengji Ointment can promote the expression of wound VEGF, bFGF and TGF- β , thus promoting the proliferation and differentiation of various tissue cells such as epidermal cells, vascular glial cells and smooth muscle cells, promoting the generation of new blood vessels and the growth of granulation tissue, and accelerating the healing of the wound.

5.3 Adjust the Expression of the Signal Path

It was found that the mechanism of action of Xiangpisheng muscle cream to promote wound healing may be to regulate the process of apoptosis through the Fas/Fas L signaling pathway, JAK2/STAT3 signaling pathway, PI3K/Akt/mTOR signaling pathway, p38/MK2 signaling pathway [37], the

proliferation, differentiation and migration. (1) Fas/Fas L signal path. Apoptosis has been confirmed to be closely related to wound repair, and the Fas/Fas L signaling pathway is the classic exogenous signaling pathway of cell apoptosis. If the cells in the granulocyte tissue during the proliferative period are excessively apoptotic, it will lead to delayed wound healing or even no healing. Therefore, the Fas/Fas L signaling pathway is a modulation An important pathway to control cell apoptosis in granulation tissue to promote wound healing [42]. Studies show that Xiangpi Shengji Ointment can reduce the relative expression of Fas, Fas L, cyto-c mRNA and Fas, Fas L, caspase-8, cyto-c eggs. The white expression level inhibits the apoptosis of wound cells after anal fistula by inhibiting the activation of the Fas/Fas L pathway, thus promoting wound healing [43]. (2) JAK2/STAT3 signal pathway. JAK2/STAT3 signaling pathway can affect the activation state of many effective molecules downstream, thus playing an important role in cell proliferation, differentiation, apoptosis, stress, inflammatory response, immunomodulation, etc. It is one of the important signal transduction pathways in the cell [44]. It is found that IL-6 can activate the JAK2/STAT3 signaling pathway, while Xiangpi Shengji paste can reduce the relative expression of IL-6 mRNA, JAK2 mRNA and STAT3 mRNA in postoperative wounds, inhibit JAK2/STAT3 signaling pathway in the wound granulation tissue after anal fistula surgery and regulate inflammatory reactions [45]. (3) PI3K/Akt/mTOR signal path. PI3K/Akt/mTOR signaling pathway is closely related to repairing damaged blood vessels and promoting angiogenesis [46]. PI3K is involved in regulating the physiological processes of cell proliferation, apoptosis and differentiation. As a downstream substrate of PI3K, Akt can ensure that a variety of growth factors play their role and function through the conduction of PI3K/Akt signaling pathway. mTOR enhances Akt's kinase activity on specific substrates, and also It can regulate angiogenesis, mitochondrial activity, lipid synthesis and glucose, amino acid and nucleotide metabolism. The PI3K/Akt/mTOR signaling pathway formed by the three provides substances and energy for wound healing, promotes the formation of new blood vessels, and is an important pathway for wound healing. According to relevant studies [47], Xiangpi Shengji Ointment increases the content of bFGF, EGF and VEGF in rats in the treatment of wounds after anal fistula surgery. Its healing mechanism may be related to regulating the expression of PI3K/Akt/mTOR signaling pathway-related proteins. It by upregulating PI3K/ Akt/mTOR signaling pathway-related protein activates PI3K/Akt/mTOR signaling pathway, reducing the wound inflammation after anal fistula surgery, promoting wound granulation growth, and accelerating the wound healing process. (4) 4p38/MK2 signal path. The p38/MK2 signaling pathway plays an important role in tissue repair. When the tissue is injured, the p38/MK2 signaling pathway is activated and stimulates the body to produce a variety of inflammatory factors such as IL-1, IL-6, TNF- α , etc., and there is a serious inflammatory reaction on the wound after anal fistula surgery. According to research, Xiangpisheng muscle cream can reduce the level of inflammatory factors, effectively inhibit the over-activation of the p38/MK2 signaling pathway, reduce the inflammatory response of the wound, and promote wound healing [31]. It can be seen that in the mechanism of wound healing after anal fistula, elephant skin ointment is closely related to Fas/Fas L signaling pathway, JAK2/STAT3 signaling pathway,

PI3K/Akt/mTOR signaling pathway, and p38/MK2 signaling pathway. By inhibiting excessive cell apoptosis, reducing the level of inflammatory factors, and enhancing the proliferation, differentiation and migration of fibroblasts and vascular endothelial cells, thus shortening the time of wound healing after anal fistula surgery, reducing the risk of inflammatory response and promoting wound healing.

6. Summary

As a commonly used traditional Chinese medicine ointment in dermatology, elephant skin ointment has been used for more than 100 years and has undergone several improvements, including the improvement of its preparation process [48-49] and the fine-tuning of the main prescription [50-51]. The increasingly developed elephant skin ointment has now played an irreplaceable role. Today, with the rapid development of modern medicine, the research on the mechanism of Xiangpi Shengji Ointment in the treatment of wound healing has also entered a new era. Xiangpi Shengji Ointment combined with simmering pus long meat method to treat wound healing. The "puscess" simmered by it can play the effect of warming meat simmering pus and growing skin. It can improve the bidirectional transportation function of endothelial cells, provide the wound with the required nutrients and their growth factors. At the same time, it also has an anti-infective effect and promote the healing of the wound. Secondly, the active ingredients of Xiangpi Shengji Ointment can regulate the expression of inflammatory factors, growth factors and signaling pathways, and jointly promote the healing of wounds in multiple ways. At present, the research on Xiangpi Shengji Ointment mainly focuses on the observation of the clinical curative effect of wound repair, and the research on its specific mechanism of action is still very limited. In-depth research can be carried out in the future to promote the development of the external treatment method of modern traditional Chinese medicine.

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