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# The Role of TNF-Alpha in the Wound Healing Process: Molecular and Clinical Perspectives - A Systematic Literature Review

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**ABSTRACT**

Wounds are conditions of damage and partial loss of body tissue caused by physical trauma, sharp objects, blunt objects, temperature fluctuations, chemical exposure. Wound healing is a complex interaction between cells, cytokines, mediators, and blood vessels as a natural physiological response to tissue damage. TNF-α has a crucial role in the wound healing process, facilitating body immunity, immune cell mobilization, fibroblast cell proliferation, keratinocytes, and growth factor expression. Although TNF-alpha has benefits in the early stages of wound healing, excessively high levels or a sustained inflammatory response can lead to problems, such as excessive scar tissue formation or blockages, which can impede the wound healing process. This study utilized the PRISMA-ScR (Scoping Review) protocol. A review was conducted of articles discussing the Role of TNF-Alpha in the Wound Healing Process: Molecular and Clinical Perspectives within the last 10 years. Literature search in this study using PubMed, ScienceDirect, Elsivier and Google Scolar databases Search using English, abstract and full text. After searching with the keywords: The Role of TNF-Alpha, 19,022 articles were found. The search continued using the keyword The Role of TNF-Alpha in the Wound Healing found 346 articles. The last search using the keyword The Role of TNF-Alpha in the Wound Healing: Molecular and Clinical found 26 articles. TNF-α plays an important role in the early stages of cutaneous wound healing, significantly delayed after day 3, but not by day 7. TNF-α has a crucial role in the early stages of skin wound healing, and its administration is recognized to have a positive impact on the healing response, which may pave the way for innovative strategies to address chronic skin wound healing problems.

## 1. Introduction

A wound is a condition of damage or partial loss of body tissue as a result of various causes. Any tissue that has anatomical integrity can be classified as a wound if it is damaged. Trauma can cause structural damage to tissues, which can be caused by physical trauma, sharp object trauma, blunt objects, temperature fluctuations, chemical exposure, explosive events, electric shock, and animal bites can involve structural damage to tissues. A thorough understanding of the cause of the wound is important for proper diagnosis and effective treatment.[1,2,3]

Injuries can occur due to certain conditions, as part of a disease process, or due to accidental or unintentional causes.[4] Trauma is a challenge that has significant clinical, social, and economic impacts.[5] As many as 8.2 million people in the United States suffer from some type of injury or wound based on data from medicare. Medicare spending on wound care is much higher than it used to be.[6]

In 2013, the Indonesian Ministry of Health reported a wound incidence rate of 8.2%, with South Sulawesi at 12.8%, compared to 4.5% in Jambi. This shows a significant disparity in wound rates in

Indonesia that requires better medical intervention. [6-8]

Contributing factors included sharp or blunt force injuries at 7.3% and other road vehicle accidents at 7.1%. This analysis provides a comprehensive picture of the distribution of injury types and causal factors in the Indonesian population, with abrasions and falls being the main concerns in the injury profile.[9]

Wound care is an important activity in the treatment of wounds or damage to the skin, mucous membranes, and tissues caused by various conditions, including trauma, fractures, and surgical wounds, with the aim of accelerating the healing process, reducing infection, and minimizing damage to the skin surface. Measures such as carefully cleaning the wound to remove debris and dead tissue, protecting the affected area from infection by using sterile dressings, and ensuring proper moisture in the wound can be an integral part of the treatment.[10,11]

Therefore, a proper understanding of the healing process is essential when managing complex wounds. A deep understanding of the healing process can improve the quality of wound care.[12] Wound healing is a natural physiological response to tissue damage that involves complex interactions between cells, cytokines, mediators and blood vessels. A wave of vasoconstriction and platelet aggregation is initiated to stop bleeding (Figure 1). Then, inflammatory cells, especially neutrophils, infiltrate and release mediators and cytokines to promote angiogenesis, thrombosis and re-epithelialization. Fibroblasts then deposit extracellular components in the healing process.[13-15]

The first phase, called the inflammatory phase, occurs within hours to days after the injury. In this phase, blood vessels around the injured area dilate, allowing blood and white blood cells (leukocytes) to reach the injured area. The second phase, the proliferation phase, takes place a few days to weeks after the injury. In this phase, new tissue formation occurs to replace the damaged area. Angiogenesis, or the formation of new blood vessels, also occurs to ensure adequate blood supply to the healing area.

The third phase, known as the remodeling or consolidation phase, occurs over a period of weeks to months, even years after the injury. In this phase, there is an adjustment and strengthening of the scar tissue formed during the proliferation phase. The collagen produced earlier is rearranged to increase the strength and elasticity of the tissue. If there is excess scar tissue, a process of reduction or thinning may occur during this phase.[16-18]

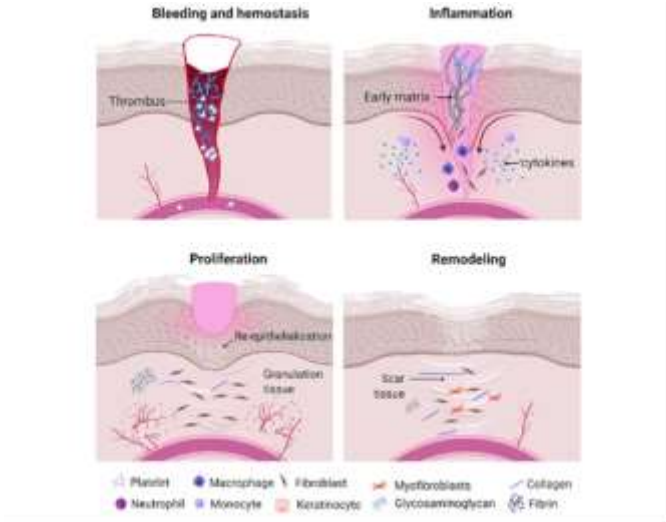


Figure 1. Wound healing process. There are four phases of wound healing, where cytokines releases including TNF alpha is secreted at the early phase such as inflammation phase.[36]

Tumor necrosis factor (TNF) is a cytokine secreted by macrophages that binds to cell surface receptors and plays an important role in maintaining immune system homeostasis. TNF-α, a type of TNF, plays an important role in the inflammatory phase of wound healing. TNF-α not only stimulates the body's immune response but also recruits immune cells to the wound site. In addition, TNF-α activates the proliferation of fibroblasts and new blood vessels, the formation of keratinocytes, and the expression of growth factors.[19,20]

During normal wound healing, tumor necrosis factor alpha (TNF-α) reaches its highest levels between 12 and 24 hours after injury. TNF-α is a cytokine that plays an important role in the immune system, and its increased concentration at this stage is associated with a significant inflammatory response aimed at removing pathogens and dead cells from the wound area. During this phase, TNF-α activity can trigger a series of biological events, including activation of immune cells, proliferation of fibroblasts, and production of growth factors that promote tissue regeneration. Structurally, TNF-α is a homotrimeric protein consisting of 157 amino acids, mainly produced by activated macrophages, T-lymphocytes, and natural killer cells. Its function is known to trigger a series of inflammatory molecules, including cytokines and other chemokines. TNF-α comes in both soluble and transmembrane forms. Transmembrane TNF-α (tmTNF-α) is a precursor form that is initially synthesized and needs to be processed by TNF-α-converting enzyme (TACE), a membrane-bound disintegrin metalloproteinase, in order to be released as soluble TNF-α (sTNF-α).[21,22]

Wound care should be simple and uniform, should be appropriate to the condition and type of wound, which lies in its ability to accelerate the healing process, prevent disruption, and lower costs and productivity. When caring for a patient's wound, nurses collaborate with other members of the medical team to assess and control external and internal factors to create an optimal healing environment.[23,24]

As an inflammatory cytokine, TNF-alpha has a major impact on the regulation of inflammatory responses and tissue healing. Although TNF-alpha is beneficial in the early stages of wound healing, excessively high levels or prolonged inflammatory responses can cause problems, such as excessive scar tissue formation, hindering the wound healing process. Therefore, this article will discuss the regulation of TNF-alpha and its balance during wound healing.

## 2. Methods

This study utilized the PRISMA-ScR (Scoping Review) protocol.25 A review was conducted of articles addressing the Role of TNF-Alpha in the Wound Healing Process: Molecular and Clinical Perspectives in the last 10 years. The literature search in this study used PubMed, Science Direct, Elsivier and Google Scolar databases. Search using English, abstract and full text.

## 3. Results

After searching with the keyword The Role of TNF-Alpha, 19,022 articles were found. The search continued using the keyword The Role of TNF-Alpha in the Wound Healing found 346 articles. The last search using the keyword The Role of TNF-Alpha in the Wound Healing: Molecular and Clinical found 26 articles.

## 4. Discussion

Scars resulting from burns, trauma and chronic diseases are a negative impact on quality of life and health, and can pose a serious economic and social burden, including medical expenses and potential limitations on social and professional activities. In other contexts, the presence of scars on a person can affect psychological aspects. This suggests that the experience of scars can affect a person's mental and emotional state.[26,27]

Wound healing is a complex and dynamic process that is divided into three main stages: the inflammatory phase, the proliferation phase, and the remodeling phase. It is important to note that these three phases do not occur in isolation. Rather, they occur simultaneously to achieve optimal wound healing.[28,29]

Tumor necrosis factor-alpha is rapidly released by vascular endothelial cells, keratinocytes and fibroblasts at the wound site. This process promotes the arrival of inflammatory leukocytes to the damaged tissue, triggering inflammation. One study that has been conducted entitled The critical role of tumor necrosis factor-α in the early process of skin wound healing showed TNF-α production peaked on the third day after injury. Wound healing was significantly delayed after day 3, but not by day seven. These results provide strong evidence that TNF-α plays an important role in the early stages of skin wound healing.[30]

TNF-α production increases significantly when chronic inflammatory diseases develop in individuals. TNF-α stimulates the inflammatory response and can cause uncontrolled inflammation around the wound when it is too much. This creates conditions that are less suitable for the wound healing process.31 Excessive TNF-α secretion can have a negative impact that can trigger uncontrolled chronic inflammation, which in turn can lead to tissue and organ damage. This chronic inflammation has been linked to a number of autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease. In addition, excessive secretion of TNF-α can also contribute to disease pathologies such as heart disease, type 2 diabetes, and cancer TNF-α, a pro-inflammatory cytokine, is responsible for activating the inflammatory response, and increased secretion of TNF-α can lead to uncontrolled and sustained inflammation around wounds, which inhibits the healing process.

According to Ritsu Masae et al.'s study, TNF-α levels tend to increase significantly in the early stages of wound healing, especially on days 1 to 3, with peak production reaching 115 pg per wound. However, on day 7 there was a decrease, which was around 70 pg per wound. Anti-TNF-alpha mAb drugs are administered to counteract the effects of TNF-alpha. In chronic wound conditions there is an excess or overactivation of TNF-alpha, this can lead to excessive inflammation and can be associated with various disease conditions, such as rheumatoid arthritis, inflammatory bowel disease, and others. Therefore, administering anti-TNF-alpha mAb drugs aims to relieve or overcome the negative effects caused by the excessive activity of TNF-alpha.

The results showed that on the third day of drug administration, there was an increase in wound closure, while the density of inflammatory cells and fibroblasts decreased. This indicated that the wound healing process was faster compared to the control group, where the mice also received IgG treatment.[30]

Based on research conducted by Ashcroft GS and colleagues, topical application of anti TNF-α antibodies in wound cases not only reduces leukocyte recruitment and NFκB activation, but also alters macrophage balance, increases matrix synthesis, and promotes the wound healing process. All of these contribute to more effective treatment of inflammation and healing Tumor Necrosis Factor-alpha (TNF-α) has very diverse roles in the context of human health. Positively, TNF-α serves as an important factor in the wound healing process, playing a key role in stimulating local inflammation, activating immune cells, and promoting cell proliferation to accelerate tissue healing. However, on the other hand, an imbalance in TNF-α production can also be a major contributor in the development of autoimmune diseases.[32,33]

An abnormal wound healing process can lead to the formation of scar tissue. Research conducted by Carlotta and colleagues explains that scar tissue

formation and delayed wound healing can result from increased levels of TNF-alpha.[34,35]

## 5. Conclusion

TNF-α plays an important role in the early stages of wound healing in the skin. Abnormal wound healing processes can lead to the formation of scar tissue. This highlights the urgency to further examine the role of TNF-α in the context of chronic wounds, prompting the need for additional research and literature to understand its substantial impact on the chronic wound healing process in humans.

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