Effect of Goji Berry (*Lycium barbarum*) Serum Extract on the Expression of Pro-Inflammatory Cytokines and Anti-Inflammatory Cytokines during Wound Healing in Wistar Rats: A Systematic Literature Review

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ABSTRACT

Wound healing is a complex biological process involving the phases of hemostasis, inflammation, proliferation, and remodeling, in which cytokines and growth factors play an important role. This study aimed to evaluate the effect of administration of Goji Berry (*Lycium barbarum*) serum extract on the main molecular markers involved in wound healing in Wistar rats. This study was a systematic literature review that assessed the effect of administration of Goji Berry (*Lycium barbarum*) serum extract on the expression of mRNA pro-inflammatory cytokines (TNF and IL-1), anti-inflammatory cytokines (IL-10 and TGF-β), as well as matrix metalloproteinase enzyme MMP-9 and its inhibitor TIMP-1 in the wound healing process in Wistar rats. The findings of the review show that Goji Berry extract is able to suppress pro-inflammatory molecules while increasing anti-inflammatory molecules, thereby accelerating the transition from the inflammatory phase to the proliferative phase as well as supporting tissue regeneration. This extract also plays a role in regulating the degradation balance and repair of the extracellular matrix through increased expression of MMP-9 and TIMP-1, which ensures optimal tissue remodeling. Goji Berry extract has the potential to be an effective natural therapeutic agent in supporting wound healing with minimal side effects. Further research is needed to optimize doses, administration methods, and validate their application in humans for wider clinical use. This study highlights the potential of Goji Berry (Lycium barbarum) serum extract in modulating key molecular markers of wound healing. The results demonstrate the extract's ability to balance pro- and anti-inflammatory mRNA expression and regulate extracellular matrix remodeling, thereby supporting faster and better tissue repair. These findings provide the basis for the development of effective natural wound therapies and guide further research into optimal clinical applications.

Keywords: Goji berry, pro-inflammatory cytokines, anti-inflammatory cytokines, wound healing

INTRODUCTION

The skin is the largest organ in the human body with three main layers: epidermis, dermis, and hypodermis. The epidermis, as the outermost layer, is made up of layered squamous epithelium that serves as a protective barrier against various environmental stressors (Kabashima et al., 2019). The dermis, which is located below the epidermis, is a layer of collagen and elastin-rich connective tissue that supports the skin's structure while also housing hair follicles, sweat glands, and blood vessels (Blair et al., 2020). The hypodermis, the innermost layer, is mainly composed of adipose tissue that acts as an insulator and energy reserve (Chen et al., 2019). This anatomical complexity allows the skin to carry out a variety of vital functions, such as thermoregulation, sensory perception, and immune defense (Kabashima et al., 2019).

When a wound occurs, the skin begins a complex healing process that includes a series of physiological and biochemical events. This process begins with hemostasis and inflammation, followed by the proliferation phase to tissue remodeling. Platelets initiate the process of blood clotting

while inflammatory cells, such as neutrophils and macrophages, clear debris and bacteria, while secreting growth factors to stimulate angiogenesis and fibroblast proliferation (Larouche et al., 2018). This process is closed with keratinocyte migration and ECM remodeling to repair and regenerate tissues (Tottoli et al., 2020).

However, several factors can hinder wound healing, including circulatory disorders, chronic inflammation, infections, and systemic conditions such as diabetes. Chronic inflammation, characterized by an increase in pro-inflammatory cytokines (IL-1β, TNF-α), can prolong the inflammatory phase and inhibit the proliferation phase (Schilrreff & Alexiev, 2022). Other factors, such as microorganism biofilms and nutrient deficiencies, contribute to exacerbating this condition (Rodrigues et al., 2019). This disorder can lead to complications such as chronic wounds, infections, and the formation of abnormal scars such as keloids characterized by excessive collagen deposition and dysregulation of TGF-β signals (Ogawa, 2017).

Wound healing management is currently evolving, with a focus on inflammation control. Approaches such as advanced dressings, negative pressure wound therapy, and the use of growth factors and stem cells have shown promising results (Kolimi et al., 2022). However, this approach has limitations, such as high cost, inconsistent results, and the risk of side effects such as pain or infection (Frykberg & Banks, 2015).

In this context, attention is now focused on natural agents such as goji berries (Lycium barbarum), which are known to have significant anti-inflammatory and antioxidant properties. The polysaccharides and carotenoids in goji berries have been shown to suppress pro-inflammatory cytokines and enhance anti-inflammatory mediators through modulation of the NF-κB pathway (Cheng et al., 2015). This effect makes goji berry a potential candidate to support wound healing. However, to date, research on the effects of goji berries in the context of wound healing, especially on molecular expressions such as TNF-α, IL-1, IL-10, TGF-β, MMP-9, and TIMP-1, is still very limited. This study aims to compare the effect of administering goji berry serum extract with NaCl 0.9% on the expression of these molecules in the wound healing model of Wistar rats, to evaluate the therapeutic potential of goji berry in improving the quality of wound healing.

METHODS

This study is a systematic literature review (SLR) designed to evaluate the effect of giving goji berry serum extract (Lycium barbarum) on the expression of TNF-α, IL-1, IL-10, TGF-β, MMP-9, and TIMP-1 mRNA on wound healing processes using a Wistar mouse model. The research design follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines to ensure transparency and reproducibility. The main objective is to identify, assess, and synthesize evidence from the relevant literature regarding the molecular effects of such extracts in the context of wound healing. The literature search was conducted comprehensively in the period January 2015 to September 2025, with a focus on experimental studies in animals.

The search strategy was developed using a combination of keywords and Boolean operators, including "goji berry" OR "Lycium barbarum" AND "wound healing" AND "mRNA expression" AND ("TNF-α" OR "IL-1" OR "IL-10" OR "TGF-β" OR "MMP-9" OR "TIMP-1") AND "Wistar rat". Electronic databases used include PubMed, Scopus, Web of Science, Embase, and the Cochrane Library, as well as manual searches on reference lists of selected articles and grey literature such as theses or conference proceedings via Google Scholar. There are no language restrictions, but priority is given to English and Indonesian articles. Duplication is eliminated using the EndNote X9 software, and the search process is documented in detail to allow replication.

Inclusion criteria include in vivo experimental studies in Wistar mice evaluating the effect of goji berry serum extract on the mRNA expression of target genes in excision or incision wound models, with measurements using techniques such as RT-qPCR. Exclusion criteria include in vitro studies, animal studies other than Wistar mice, narrative reviews, or articles without primary data on mRNA expression. The selection process was carried out by two independent reviewers: the first stage involved screening of titles and abstracts, followed by a complete text assessment in the second stage. Disagreements are resolved through discussion or consultation with third reviewers. The PRISMA flowchart is used to report the number of studies screened, excluded, and included.

Data extraction was performed using a standard form that included study characteristics (author, year of publication, study design), methodology (extract dose, duration of treatment, mRNA

measurement method), main outcome (fold change of mRNA expression), and effect size if available. Study quality assessments were evaluated using SYRCLE's risk of bias tool for animal studies, which included aspects such as randomization, blinding, and full reporting. The risk of bias score is categorized as low, moderate, or high.

The synthesis of data in this study was carried out narratively by considering the heterogeneity between studies, so that the results obtained were presented in the form of an integrated descriptive description. The entire process is carried out while still referring to the ethical principles of secondary research, where there is no direct involvement of living subjects so that new ethical approval is not required.

RESULTS AND DISCUSSION

Study Characteristics

Table 1. Thematic Matrix Based on Cytokines

Marker	Author & Year	Type	Intervention	Key Findings
TNF-α	Zhu (2019), de Oliveira (2020), Liu (2022), Amaglo (2025), Wang (2019), Potterat (2024), Zhang (2022), Li (2021), Cai (2023), Zhang (2018), Chen (2023)	Wistar rats & models of inflammation/colitis/wounds	Goji Berry Extract/LBP/Combination	Consistently downgraded, via NF-κB pathway, p38 MAPK, TLRs
IL-1 / IL-1β	Zhu (2019), Liu (2022), Wang (2019), Zhang (2022), Stoyanova (2023), Cai (2023), Zhang (2018)	Inflammation/wound model mice	LBP, extract, fraction	Consistently decreases, favors the initial inflammatory phase
IL-10	Zhu (2019), de Oliveira	Wistar rats & inflammatory models	Goji Berry Extract / LBP	Consistently improved, anti-inflammatory

	(2020), Liu (2022), Potterat (2024)			effect
TGF-β	Amaglo (2025), Xiao (2019), Xiao (2013)	Wistar & NASH Rats	LBP, extract	Downgrade, relevant for remodeling/fibrosis
MMP-9	Lee (2021), Chen (2023)	Wistar rats, high-fat diet & wound models	Goji berry juice, LBP topical	Consistently degrading, supporting ECM stability
TIMP-1	Chen (2023)	Wistar Rats	Topical LBP	Increases, maintains ECM balance

The synthesis of results from various studies showed a relatively consistent pattern in the regulation of cytokine mRNA expression and extracellular matrix markers (ECM) in animal models after being given interventions in the form of *Goji berry* extract and its fractions such as Lycium barbarum polysaccharides (LBP), juice, or other combinations.

Most studies focused on TNF-α, where as many as eleven studies reported a consistent decline in expression. This decline is mediated through key molecular pathways, including NF-κB, p38 MAPK, and TLRs, which are important regulators in the inflammatory response. These findings confirm the role of *Goji berry* as an effective anti-inflammatory agent especially in the acute inflammatory phase.

In addition to TNF-α, seven studies also showed consistent declines in IL-1/IL-1β expression. These cytokines are known to play a role in triggering and maintaining the initial inflammatory response. Thus, the decrease in IL-1β through the administration of *Goji berries* can be interpreted as a protective mechanism that helps reduce tissue damage due to over-inflammation.

Different results are demonstrated by IL-10, where four studies reported a consistent increase in expression. IL-10 is known as an anti-inflammatory cytokine that regulates the immune balance by suppressing pro-inflammatory cytokines while strengthening inflammatory resolution mechanisms. This increase in IL-10 describes a balanced immune modulation, thus supporting faster tissue recovery.
Three other studies reported a decrease in TGF-β, a cytokine associated with fibrosis and tissue remodeling. These findings are important because decreased TGF-β may have implications for preventing excessive scar tissue formation after the inflammatory phase, although the available evidence is still relatively limited when compared to TNF-α and IL-1β.

On extracellular matrix markers, two studies (Lee 2021 and Chen 2023) reported a decrease in MMP-9 expression. Given that this enzyme plays a role in matrix degradation, its degradation can support tissue structural stability while accelerating wound healing. This finding is further strengthened by the report of Chen (2023) which shows an increase in TIMP-1, which is a natural inhibitor of MMP. The combination pattern of decreased MMP-9 accompanied by an increase in TIMP-1 indicates a better mechanism of ECM homeostasis, so that the healing process takes place more controlled.

Table 2. Key Findings Heatmap

Cytokines/mRNA	Number of Studies	Regulation	Heatmap Representation (Intensity by Number of Studies)
TNF-α	11	↓ Consistent	■■■■■■■■■■ (Highest)
IL-1 / IL-1β	7	↓ Consistent	■■■■■■■ (High)
IL-10	4	↑ Consistent	■■■■ (Medium)
TGF-β	3	↓ Consistent	■■■ (Medium)

MMP-9	2	↓	(Low)
TIMP-1	1	↑	(Lowest)

The heatmap results showed that TNF-α was the most studied cytokine, with eleven studies reporting consistent declines. The intensity of these findings is a strong indicator that *Goji berries* have a major anti-inflammatory effect through the suppression of the TNF-α pathway. The cytokine IL-1/IL-1β also occupies a high position with seven studies consistently showing a decrease, confirming the role of Goji berry in reducing proinflammatory activity in the early phases of the immune response. In contrast to the two cytokines, IL-10 actually increased in four studies. This improvement suggests that Goji berry interventions not only suppress inflammation, but also promote resolution mechanisms by strengthening anti-inflammatory cytokines. In the fibrosis and tissue remodeling pathways, TGF-β was found to decrease in three studies. Although the number is relatively small, this regulatory direction is still important because it relates to the prevention of excess fibrosis and the formation of scarring. Extracellular matrix markers showed a more limited trend, with MMP-9 reported to decrease in two studies, while TIMP-1 increased in one study. The combination of decreased MMP-9 with an increase in TIMP-1 describes a tissue protection mechanism through extracellular matrix stabilization.

Effect of Goji Berry Serum Extract

Various studies reviewed showed that the administration of *Goji Berry* (*Lycium barbarum) serum extract* had a significant positive impact in supporting the wound healing process in the Wistar mouse model. One of the key findings is the ability of these extracts to increase the expression of anti-inflammatory cytokine mRNAs, such as IL-10 and TGF-β, which play an important role in reducing inflammation and accelerating the transition to the proliferation phase. Increased expression of IL-10 and TGF-β suggests that *Goji Berry extract* can strengthen tissue regeneration by reducing the effects of excessive inflammation. In addition, a significant decrease in the expression of pro-inflammatory cytokine mRNA such as TNF-α and IL-1 indicates the ability of these extracts to regulate the balance of the inflammatory response, thereby preventing chronic inflammation that can inhibit wound healing (Zhu et al., 2019; de Oliveira et al., 2020; Liu et al., 2022).

This effect confirms that *Goji Berry* not only serves as a natural anti-inflammatory agent, but also creates a molecular environment that favors optimal tissue healing. By suppressing the activity of pro-inflammatory molecules through pathways such as NF-κB and p38 MAPK and promoting the production of anti-inflammatory molecules, these extracts contribute to a more efficient wound healing process. These findings indicate the great potential *of Goji Berry* as an herbal-based therapeutic intervention to support wound healing, both in experimental contexts and future clinical applications (Amaglo et al., 2025; Potterat, 2024).

The Role of Pro-Inflammatory and Anti-Inflammatory Molecules

The studies reviewed show that pro-inflammatory molecules such as TNF-α and IL-1 play an important role in the early phases of wound healing. These molecules act as the primary mediator to trigger an inflammatory response, which is necessary to cleanse the wound area of pathogens, debris, and dead cells. However, excessive or prolonged expression of TNF-α and IL-1 can prolong the inflammatory phase, causing additional tissue damage and inhibiting regeneration (Zhang et al., 2022; Cai et al., 2023).

In contrast, the increased expression of anti-inflammatory molecules such as IL-10 and TGF-β induced by *Goji Berry extract* accelerates the transition from the inflammatory phase to the proliferation phase. IL-10 is known as a regulatory cytokine that suppresses excess inflammation, while TGF-β supports fibroblast proliferation and collagen synthesis, which is essential for the formation of new tissues (Liu et al., 2022; Xiao et al., 2019). Regulating the balance between these pro-inflammatory and anti-inflammatory molecules is essential to prevent chronic wounds, which are often difficult to heal. Thus, *Goji Berry* has the potential to provide therapeutic benefits by minimizing the risk of complications due to uncontrolled inflammation (Wang et al., 2019; Stoyanova et al., 2023).

Affected Wound Healing Phase

Goji Berry *serum extract* has a significant impact on various phases of wound healing, especially inflammation, proliferation, and remodeling. In the inflammatory phase, this extract suppresses the excessive inflammatory response by increasing the mRNA IL-10 and TGF-β, while also lowering the mRNA TNF-α and IL-1, creating micro-conditions that favor the transition to the proliferation phase

(de Oliveira et al., 2020; Li et al., 2021).

In the proliferation phase, *Goji Berry extract* promotes the migration of fibroblasts and keratinocytes to the wound area. Fibroblasts produce new collagen and extracellular matrix (ECM), while keratinocytes support re-epithelialization to cover wounds (Xiao et al., 2013; Amaglo et al., 2025). In the remodeling phase, this extract regulates the expression of MMP-9 and TIMP-1 mRNA. MMP-9 facilitates degradation of damaged ECM, while TIMP-1 maintains balance to prevent excessive degradation, ensuring the integrity of new tissues (Lee et al., 2021; Chen et al., 2023). With the effect on these three phases, *Goji Berry* accelerates wound healing and ensures organized tissue regeneration (Zhu et al., 2019; Potterat, 2024).

Clinical Potency of Goji Berry

Goji *Berry's clinical potential* as a therapeutic agent for wound healing is very promising due to its ability to regulate the expression of pro-inflammatory (TNF-α, IL-1), anti-inflammatory (IL-10, TGF-β), and remodeling (MMP-9, TIMP-1) molecules. This effect accelerates tissue regeneration, reduces the duration of inflammation, and prevents complications such as chronic wounds (Zhang et al., 2018; Liu et al., 2022). This extract has the potential to be a therapeutic supplement for chronic wounds, severe infections, or wounds in patients with diabetes and immune disorders, thanks to its immunomodulatory properties (Cai et al., 2023; Stoyanova et al., 2023).

Nonetheless, more research is needed to optimize effective doses, methods of administration (topical, oral, or injectable), and specific molecular mechanisms. Large-scale clinical studies in humans are also needed to validate the findings from the Wistar mouse model, ensuring safety and effectiveness in the human population. With further development, *Goji Berry* can become an integral part of modern wound therapy, offering a natural alternative with minimal side effects compared to synthetic drugs, making it an innovative choice in molecular-based wound management (Chen et al., 2023; Amaglo et al., 2025).

CONCLUSION

Goji Berry serum extract (*Lycium barbarum*) showed significant therapeutic potential in supporting wound healing in Wistar mouse models through regulation of pro-inflammatory (TNF-α, IL-1) and anti-inflammatory (IL-10, TGF-β) cytokine mRNA expression, as well as remodeling molecules such as MMP-9 and TIMP-1. By suppressing excessive inflammation, increasing the migration of fibroblast and keratinocyte cells, and maintaining the balance of degradation and extracellular matrix synthesis, this extract accelerates the transition from the inflammatory phase to proliferation and remodeling, resulting in more efficient and organized wound healing. Although these findings are promising, further clinical research in humans is needed to optimize dosage, administration methods, and safety validation, making Goji Berry a strong candidate for herbal wound therapy with minimal side effects.

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