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Clinical applications and progresses of Tripterygium wilfordii extracts in treatment of systemic lupus erythematosus

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Abstract:

Tripterygium wilfordii Hook. F (TW), commonly known as Thunder God Vine, is a perennial woody vine belonging to the Celastraceae family and has long been used as a traditional Chinese medicinal herb. It possesses a wide range of pharmacological activities, including potent anti-inflammatory effects, the ability to modulate immune responses by regulating immune cell activity and cytokine secretion, and the capacity to induce apoptosis specifically in abnormal or pathological cells. Clinically, its application is particularly prominent in the treatment of various autoimmune diseases, with systemic lupus erythematosus (SLE) being one of the key conditions it targets. Previous research studies have sufficiently demonstrated the therapeutic efficacy of extracts derived from TW in the management of SLE; however, the inherent toxicity of these extracts has significantly restricted their widespread adoption and long-term use in clinical practice. This article aims to systematically review the underlying pathological mechanisms of SLE and summarize the important clinical advances made over the past five years regarding the application of specific *Tripterygium wilfordii* extracts—namely tripterygium glycosides (TGs), triptolide (TP), and celastrol (CEL)—in the treatment of SLE.

Keywords: *Tripterygium wilfordii* extracts; systemic lupus erythematosus; clinical applications; celastrol

1. Introduction

Systemic Lupus Erythematosus(SLE) is a chronic autoimmune disease, characterized by multi-organ injury resulting from immune cascades. Its common clinical manifestations include erythematous rash(skin), proteinuria(renal), arthritis(musculoskeletal), lupus cerebritis(nervous), peritonitis(gastrointestinal), interstitial lung disease(pulmonary), pericarditis(cardiovascular) and so on. According to reports, SLE exhibits tendency related to gender, age, and geography, with a higher incidence observed among African American women aged 15-44 [1].

There are various perspectives regarding the etiology

and pathogenesis of SLE. In the field of traditional Chinese medicine (TCM), the theory of innate constitutional deficiency is widely accepted by most practitioners. This theory posits that SLE stems from the interaction of external factors(such as pathogenic heat) and internal factors (primarily innate constitutional deficiency). In other words, against a background of internal deficiency, the invasion of external adverse stimuli (heat-toxins)can trigger the disease mechanisms, leading to stasis obstructing the meridians and organ damages. For an extended period, traditional Chinese medicine therapies, notably those involving TW and their chemical constituents, have been utilized in the management of SLE. Although glucocorticoids have long formed the foundation of SLE treatment and shown considerable effectiveness in curbing disease progression, their use is associated with substantial adverse effects [2]. This paper reviews existing literature on the clinical advances of chemical components derived from TW, as well as the pathogenic mechanisms underlying SLE.

2. Pathogenesis of SLE

Due to variations in multifaceted factors among patients, SLE show apparent heterogeneity. In this case, pathogenesis of SLE is complicated and still remains incompletely elucidated at present but it has been proved to be associated with genetic, immunological, and environmental factors. Consequently, the production of auto-antigens that attack the body's own cells in SLE patients leads to a breakdown of immune tolerance and induces hyperactivity in both the adaptive and innate immune systems. The immune complexes formed during this process deposit in various tissues, leading to chronic inflammation and dysfunction of organs [3].

2.1 Endogenous Biological Process

2.1.1 Aberrant Activation of Immune Cells

Generally, our immune system possess a series of self-tolerance mechanisms(central and peripheral) to recognize and eliminated self-reactive immune cells, protecting our body in the absence of infection. The loss of central tolerance can lead to abnormal differentiation and expansion of B cells and T cells.Its main mechanisms in SLE include: 1) aberrant expression of Toll-like receptor 7 (TLR-7) and Toll-like receptor 9 (TLR-9) on B cells target antigens on double-stranded DNA and RNA, leading to the formation of immune complexes. 2) rapid proliferation of B cell and differentiate into long-lived plasma cells (LLPCs), which persistently produce autoantibodies. 3) multi-receptor engagement between autoreactive B cells and T cells perpetuates immune deregulation and promotes the excessive secretions of several inflammatory cytokines such as TNF-α, IL-17, IL-4, and IFN-γ.

Besides, the loss of peripheral tolerance is shown to relate with neutrophil dysfunction. Its main mechanisms in SLE include:1) impaired phagocytosis ability to clear apoptotic cells, 2) abnormal secretion of type-I IFNs in the absence of stimuli,3) low-density granulocytes(LDGs) elevated in SLE patients with tendency to form neutrophil extracellular traps(NETs) that can cause autoreactive immune response.

The deposition of immune complexes, together with neutrophil dysfunction and chronic inflammation mediated by these cytokines, contributes to the development and progression of systemic lupus erythematosus [3].

2.1.2 Genetic Predisposition

SLE has been verified to have high heritability, reflected in the distinct prevalence rates and severity across different regions. Through comparative studies of different ancestral populations and SLE patient cases, it discovered that the total number of SLE-associated genetic loci with function of antibody production exceeds 100 currently. This statistic data underscore a direct correlation between genetic factors and SLE [4]. Furthermore, both genetic polymorphisms and epigenetic disruptions are shown to increase the risk of developing SLE. For instance, the missense variant in the TNFRSF13B gene, which encodes a BAFF receptor, can lead to abnormal immunoglobulin production.

2.2 External Stimuli

Based on studies psychosocial stressors (such as anxiety, poverty, adverse childhood experiences, discrimination, etc.), a typical environmental factor, are highly associated with the onset of systemic SLE. These adverse factors can interact with genetic predispositions, thereby influencing gene expression and modulating genetically mediated responses. Furthermore, such stressors may synergize with immune factors, leading to immune dysregulation, increase in-pro-inflammatory cytokines due to sympathetic nervous system over-activation and abnormal activation of signaling pathways such as IFN and NF-κB. The combined effects collectively contribute to the pathogenesis of SLE [5].

3. Applications of TW

According to multiple ancient texts, TW is described as possessing an acrid and bitter taste and a cool nature. Most medicinal products containing TW are prepared from its roots. Upon administration, they are known to

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reduce pathogenic heat, unblock meridians, and eliminate dampness, etc.

In light of current scientific researches, various chemical constituents in *Tripterygium wilfordii*—containing diterpenoids, triterpenoids, and alkaloids—have shown significant effects in regulating or suppressing pathological inflammatory factors, signaling pathways, hormone levels, and the self-reactivity of immune cells. These compounds contribute to its multifaceted pharmacological activities, such as insecticidal, anti-inflammatory, immunomodulatory, neuroprotective, anti-angiogenic, and anti-fibrotic actions. Consequently, it has been widely used in treating conditions caused by immune dysregulation and inflammation, such as SLE,rheumatoid arthritis, psoriasis, and purpuric nephritis [6].

However, pathological studies indicate that the entire plant of *Tripterygium wilfordii* is highly toxic, ranking as a strongly toxic Chinese medicinal herb. Its toxicity, at equivalent doses, far exceeds that of other subspecies within the same family. In this case, its toxicity must be carefully considered for potential clinical application. Strategies such as herbal compatibility, combination with Western medicine, dosage form optimization, acupuncture, or moxibustion may be utilized to reduce toxicity and enhance its efficacy [7].

4. Mechanisms and Clinical Processes of TW Extracts in the Treatment of SLE

Although the specific etiology of SLE remains unclear, the multiple constituents, targets, and mechanisms associated with *Tripterygium wilfordii* extracts demonstrate potential therapeutic feasibility in regulating inflammatory pathways and autoimmune system activity, thereby having been widely employed in clinical trials for SLE.

4.1 Tripterygium Glycosides

Tripterygium glycosides (TGs) is a liposoluble total glycoside extracted and formulated from the peeled root of TW . Its primary constituents include the diterpenoid triptolide (also known as tripdiolide) and the triterpenoid celastrol, which serve as the major active compounds for the treatment of SLE .Due to various pharmacological properties, it has been extensively used in both animal studies and human clinical trials, mainly focused on suppressing aberrant immune cells and inflammatory signaling pathways associated with SLE. However, the application of TGs continues to be challenged by its toxicity profile [8].

4.1.1 Monotherapy

A study by Chen et al demonstrated that TGs can inhibit the IL-7 signaling pathway and the differentiation of Th17 cells to delay the onset of SLE [9]. The results of his animal experiment that TGs has been shown to significantly improve skin lesions, reduce pathogenic inflammatory cytokines, and suppress the aberrant differentiation of immune cells. However, it may induce hepatotoxicity and cause liver injury in clinical use. Therefore, when TP is applied as a monotherapy in clinical practice, its therapeutic benefits must be carefully balanced against its potential toxicity.

4.1.2 Combination therapy

The aforementioned case illustrates that the potential hepatotoxicity, nephrotoxicity, and reproductive toxicity of TGs may limit its applicability in SLE treatment. Therefore, current clinical practices often adopt combination regimens with other drugs to enhance therapeutic efficacy or reduce the toxicity of TGs-based therapy.

In a study by Yi Wang [10], a four-month clinical trial was conducted with a control group receiving prednisone acetate tablets and an observation group receiving TGs tablets combined with prednisone acetate. The results showed clinical effective rates of 88.89% and 65.22% in the observation and control groups, respectively, and post-treatment comparisons revealed that the observation group receiving TGs exhibited significantly greater reductions in SLEDAI scores and serum levels of IL-6 and IL-18 than the control group. These findings reflect that TGs tablets can reduce inflammatory cytokines secreted by T cells and regulate immune responses, supporting the feasibility of TGs as an adjunct therapy in clinical practice.Furthermore, a study by Yu et al demonstrated that combination therapy with TGs, glucocorticoids, and Mupirocin Ointment observably enhanced anti-inflammatory and immunomodulatory effects [11]. This was reflected in the regulation of T lymphocyte subset levels and reduced release of inflammatory mediators such as IgE. The total effective rate of the combination therapy group was considerably higher than that of the control group (97.73% vs. 79.55%), while the incidence of adverse reactions was significantly lower (4.45% vs. 25.00%), indicating favorable clinical applicability.

4.2 Triptolide

Triptolide (TP), also known as tripdiolide, is an epoxy-diterpene lactone compound derived from the traditional Chinese medicine TW. Akin to other TP has been demonstrated to possess remarkable pharmacological properties, including anti-inflammatory, anticancer, signaling pathway modulation, and immunosuppressive effects. As a result, it is increasingly being utilized in clinical settings—for instance, by inhibiting the NF-κB signaling pathway or suppressing the IL-17 inflammatory cytokine pathway

to mitigate the onset and progression of SLE. However, clinical applications should consider strategies for toxicity reduction to ensure drug safety due to its hepatotoxicity, nephrotoxicity, cardiotoxicity, and reproductive toxicity [12].

In a murine study conducted by Zhang et al, three groups of mice—a control group, a low-dose TP group, and a high-dose TP group—were administered the compound via gavage administration for eight weeks [13]. The study evaluated serum indicator levels, pathological changes, expression levels of TLR7 mRNA and miR-146a under miR-146a inhibition, as well as protein levels including TLR7 and phosphorylated NF-κB p65 (p-NF-κBp65). The results demonstrated that TP can upregulate miR-146a to modulate the Toll-like receptor and NF-κB signaling pathways without inducing significant hepatorenal toxicity. These suggest that TP may interfere with the pathogenic mechanisms of SLE mediated through these pathways, indicating favourable clinical potential.

4.3 Celastrol

Celastrol(CEL), also known as celastrine, is a pentacyclic triterpenoid compound extracted from the root bark of the traditional Chinese medicine TW, presented as a red powder. Due to its diverse biological activities, low toxicity, and multi-target characteristics, it has spotlighted in the clinical treatment of SLE. Similar to TGs and TP, CEL also demonstrates the ability to suppress autoimmune responses, inflammatory cytokines, and abnormal signaling pathways in SLE patients. Research by Xiang et al indicated that CEL exhibits inhibitory effects on the expression of pro-inflammatory factors, modulates the frequency of Treg immune cells, and reduces $CD3^+$ T cell infiltration in mouse models, thereby alleviating organ damage caused by SLE [14].

Additionally , Xie et al conducted a 20-week experiment involving MRL/lpr lupus-prone mice and MRL/MPJ mice (control group) [15]. They were randomly divided into four treatment groups: vehicle, low-dose celastrol, high-dose celastrol, and prednisone. After euthanasia at week 20, serum, lymph nodes, spleen, and kidney samples were collected for analysis.Using ELISA and Luminex platforms to measure serum biomarkers, it was found that celastrol significantly reduced levels of multiple cytokines (such as IL-6, IFN-γ, and TNF) and antibody subsets (including dsDNA IgG antibodies) in the serum of MRL/lpr mice.Other results demonstrated that CEL as a monotherapy could ameliorate multiple aspects of lupus by preventing autoimmune responses. Mechanisms included reducing the frequency of germinal center B cells and central memory T cells, as well as promoting apoptosis of $CD138^+$ cells to suppress autoreactive immune activity. Notably,in the study, CEL showed comparative advantages over prednisone in certain aspects.

5. Conclusion

With ongoing exploration into the pathological mechanisms and influencing factors of SLE, more advanced treatment strategies have been applied in both targeted animal experiments and clinical practices for SLE. Among these, TWE have been demonstrated in numerous studies to exhibit efficacy in inhibiting various inflammatory signaling pathways and aberrant autoimmunity in SLE,owing to their diverse pharmacological mechanisms. However, current research has yet to fully elucidate their overall efficacy profile , and their documented toxicities (renal, hepatic, and reproductive) remain to be completely detoxified. Therefore, further investigations into the mechanisms of action and toxicity of its active constituents are still required, which would provide new perspectives for future clinical applications and maximize their therapeutic potentials while ensuring safety.

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