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Original Research Article

Immunomodulatory Effects of *Tripterygium wilfordii* in Diabetes: Mechanisms and Therapeutic

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Abstract

Background and Objectives: To systematically evaluate the therapeutic potential and underlying mechanisms of *Tripterygium wilfordii* Hook F. (TwHF) and its active constituents, particularly celastrol and triptolide, in autoimmune and metabolic disorders, with a focus on diabetes and its complications.

Materials and Methods: A comprehensive review of recent preclinical and clinical studies was conducted, highlighting the pharmacological effects of TwHF in autoimmune diseases such as rheumatoid arthritis and psoriasis, as well as its emerging applications in metabolic conditions like diabetes. Mechanistic insights were drawn from molecular and cellular studies, and clinical data were summarized to assess efficacy and safety.

Results: TwHF exhibits multi-target immunomodulatory effects. Celastrol was found to improve insulin resistance by modulating the carbohydrate response element-binding protein (ChREBP)–thioredoxin-interacting protein (TXNIP) axis and to alleviate diabetic complications by inhibiting inflammatory pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK). Clinical trials have shown that TwHF extracts significantly reduce proteinuria in diabetic nephropathy patients. However, potential toxicity remains a concern and limits broader clinical application.

Conclusion: *T. wilfordii* and its key constituents hold promise as therapeutic agents for autoimmune and metabolic diseases due to their potent immunoregulatory properties. Further research is needed to optimize efficacy and safety, particularly for long-term use in diabetes-related conditions.

Keywords

Tripterygium wilfordii, Tripterygium derivatives, diabetes

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Introduction

Tripterygium wilfordii Hook F. (TwHF), a traditional medicinal plant from the Celastraceae family, has a significant role in the repository of Chinese herbal medicine. Since the initial isolation of the pentacyclic triterpenoid celastrol in 1936, researchers have identified and validated more than 450 chemical constituents from this plant, predominantly comprising biologically active triterpenoids (e.g., triptolide and celastrol), alkaloids, sesquiterpenes, and polysaccharides (Liu, 2011; Zhou et al., 2005; Ziaei & Halaby, 2016). These bioactive constituents demonstrate extensive immunomodulatory functions via multi-target mechanisms, including the regulation of T/B lymphocyte proliferation and activation, modulation of Th1/Th17/Treg cell subset balance, suppression of monocyte-macrophage inflammatory responses, and influence on the production of various cytokines (e.g., tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-17) (Chang et al., 1997; Luo, Zuo et al.,2019).

Due to its distinctive immunomodulatory characteristics, *T. wilfordii* and its extracts have been extensively utilized in the management of several autoimmune disorders, such as rheumatoid arthritis (RA) (Fan et al., 2018), psoriasis (Han et al., 2012), systemic lupus erythematosus (SLE) (Patavino & Brady, 2001), and human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) (Wan & Chen, 2014). Recent studies indicate that bioactive

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compounds from Tripterygium not only effectively inhibit excessive immune responses but also significantly contribute to the prevention and treatment of diabetes and its complications by enhancing insulin resistance, safeguarding pancreatic β-cell function, and alleviating chronic inflammation.

T. wilfordii in Autoimmune Diseases

Rheumatoid Arthritis

RA is the predominant autoimmune arthritis of indeterminate origin. The pathophysiology of RA entails interactions between elements of innate and adaptive immune responses, resulting in joint destruction, dysfunction, and deformity (Luo, Song et al., 2019). Standard interventions for RA encompass surgical procedures, pharmacological therapy, and psychological counseling, with pharmacological therapy being categorized into nonsteroidal anti-inflammatory medications (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and glucocorticoids (Mota et al., 2013).

The processes via which TwHF extract may treat RA are exceedingly intricate. TwHF and its active constituents can induce T cell apoptosis, inhibit Th17 cell differentiation, suppress dendritic cell maturation, reduce fibroblast-like synoviocyte infiltration, decrease Th1 cell proportion, and inhibit the expression and production of various cytokines, including IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-18, IL-18R, TNF-α, interferon (IFN)-γ, soluble intercellular adhesion molecule (sICAM)-1, chemotactic cytokines (CCL)-1, CCL-2, CCL-5, prostaglandin E2 (PGE2), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, as well as microRNA (miR)-155 and matrix metalloproteinases (MMP)-1, MMP-3, MMP-9, MMP-13. They can nitric oxide (NO) synthesis while enhancing the expression of transforming growth factor (TGF)-β, tissue inhibitors of metalloproteinase (TIMP)-1, TIMP-2, suppressor of cytokine signaling (SOCS)-1, SH2-containing inositol phosphatase (SHIP)-1, signal transducers and activators of transcription (STAT-5), and granulocyte-macrophage colony stimulating factor (GM-CSF). The effects encompass various signaling pathways, including the toll-like receptor (TLR)4/nuclear factor-κB (NF-κB) pathway, the osteoprotegerin (OPG)/receptor activator of NF-κB (RANK)/receptor activator of NF-κB ligand (RANKL) signaling pathway, and the IL-1β-mediated mitogen-activated protein kinase (MAPK) downstream signaling pathways (Wang et al., 2016). Furthermore, TwHF demonstrates significant anti-angiogenic properties (Kong et al., 2013). It modulates immunological function, maintains bone homeostasis, alleviates synovial inflammation and joint degradation, and prevents further bone damage and erosion, thereby countering RA.

In clinical trials, TwHF has demonstrated enhancement in American College of Rheumatology 20% response (ACR20), ACR50, and ACR70 response rates among RA patients, as well as a reduction in swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) levels (Luo, Song et al., 2019). In patients with active RA, a comparison of clinical indicators and imaging data revealed that TwHF monotherapy was not inferior to methotrexate monotherapy in managing RA disease activity and delaying progression (Zhou, Zhao, Chen et al., 2018), while the TwHF-methotrexate combination demonstrated superiority over methotrexate monotherapy (Lv et al., 2015). Moreover, in active RA patients who sustained consistent dosages of oral prednisone or NSAIDs for 24 weeks, the TwHF extract cohort had markedly superior ACR20 response rates compared to the sulfasalazine cohort (Goldbach-Mansky et al., 2009).

The standard therapeutic dosage of TwHF for RA is 30–60 mg per day, divided into three daily administrations (Lv et al., 2015; Zhou, Zhao, Chen et al., 2018). Combination therapy mostly consists of methotrexate, leflunomide, tocilizumab, and other DMARDs (Lv et al., 2015; Zhou, Xia, Peng et al., 2018). The topical use of Tripterygium glycosides demonstrates specific therapeutic effects on RA (Cibere et al., 2003). Nonetheless, not all RA patients derive equal benefit from TwHF-based therapies. Research has identified three positively correlated symptoms (diuresis, hyperhidrosis, night sweats) and two negatively correlated symptoms (yellow tongue coating and arthralgia) as predictors of therapy response, with enhanced efficacy noted in patients displaying the former symptoms (Jiang et al., 2015). Circulating miR-146a levels correlate with RA risk and disease activity, potentially serving as a significant predictor of clinical response to TwHF in RA patients (Chen et al., 2017). To enhance precision medicine in RA treatment, researchers have created a partial least squares model utilizing the expression levels of six candidate gene biomarkers (myxovirus (influenza virus) resistance 1 (MX1), 2′,5′-oligoadenylate synthetase-like (OASL), serine peptidase inhibitor Kazal type 1 (SPINK1), V-crk sarcoma virus CT10 oncogene homolog (avian) (CRK), GRB2-related adapter protein-like (GRAPL), and ring finger protein 2 (RNF2)) to forecast the prognostic value of Tripterygium glycosides tablets in patients with RA (Zhang, Wang et al., 2018). Moreover, research indicates that a support vector machine model utilizing four miR biomarkers (hsa-miR-550b-2-5p, hsa-miR-4797-5p, hsa-miR-6509-5p, and hsa-miR-378g) can function as a prediction model for the therapeutic efficacy of Tripterygium glycosides tablets in RA (Hu et al., 2019).

Psoriasis

Psoriasis is a chronic, recurrent, autoimmune-mediated, inflammatory skin disease, a multifactorial, disabling disorder caused by interactions between genetic and environmental triggers (Zuccotti et al., 2018), involving various immune cells, immune-related cytokines, and inflammatory mediators. It is characterized by excessive proliferation and abnormal differentiation of keratinocytes, resulting in persistent localized erythematous scaly plaques (Lowes et al., 2007).

Studies have shown that TwHF can upregulate the expression of miR-126 by inhibiting activated inflammatory mediators such as T lymphocytes and TNF-α, thereby suppressing psoriatic inflammation and maintaining skin immune homeostasis (Duan et al., 2019). Plasma miR-126 levels are negatively correlated with psoriasis health risk and severity, and its baseline level can serve as a biomarker to predict the clinical efficacy of TwHF combined with acitretin in psoriasis treatment. Tripterygium glycosides can reduce serum levels of IL-6, IL-17, and IL-23, regulate the immune function of Th17 lymphocytes in psoriasis treatment, and decrease the psoriasis area and severity index (PASI) in patients with plaque psoriasis (Luo, Zuo et al., 2019). TwHF also demonstrates excellent therapeutic effects on plaque, pustular, and erythrodermic psoriasis (Asano et al., 1998). A randomized clinical trial comparing the outcomes of 115 patients after 8 weeks of treatment found that TwHF exhibited comparable efficacy to the classic psoriasis drug acitretin in treating plaque psoriasis (Wu et al., 2015). Wang et al. conducted a retrospective analysis of hospitalized patients aged 14 years or younger with acute generalized pustular psoriasis between 2005 and 2014 and found that 11 patients responded well to TwHF treatment, indicating its potential use in pediatric patients with acute generalized pustular psoriasis (Wang et al., 2017).

Currently, TwHF serves as an alternative treatment for psoriasis. The conventional oral dosage of TwHF extract for plaque psoriasis is typically 30–60 mg/day, administered three times daily (Duan et al., 2019; Wu et al., 2015). Some studies have used a dosage of 10 mg three times daily, while others have employed Tripterygium glycoside capsules at 6 g three times daily. In terms of combination therapy, research suggests that TwHF extract yields superior outcomes when used in conjunction with glycyrrhizic acid, retinoids, or compound amino acid polypeptide tablets (Lv et al., 2018).

Systemic Lupus Erythematosus

SLE is a chronic autoimmune inflammatory disease that can affect one or multiple organ systems, characterized by high levels of circulating autoantibodies with a complex pathogenesis potentially related to genetic, endocrine, infectious, immune abnormalities, and environmental factors (Patavino & Brady, 2001).

Animal studies indicate that triptolide can restore impaired lymphocyte proliferation responses induced by concanavalin A or lipopolysaccharide, lower antinuclear antibody levels, reduce elevated plasma IL-10 and NO, alleviate proteinuria, and mitigate kidney damage in mouse models of SLE. Triptolide at 12 mg/kg demonstrated effects similar to prednisone at 5 mg/kg in treating experimental SLE, and showed better efficacy in reducing antinuclear antibodies (Li et al., 2005). Celastrol can reduce urinary protein excretion and serum anti-dsDNA antibodies in SLE mice (Xu et al., 2003), improve clinical symptoms and survival rates in SLE mice, exhibiting good therapeutic effects on SLE.

TwHF therapy, one of the most extensively researched herbal remedies for SLE treatment, can reduce NF-κB activity in SLE patients, hence producing immunosuppressive effects (Luo, Zuo et al., 2019). A case report showed (Wang et al., 2015) that a patient with plaque psoriasis incidentally progressed to associated SLE, and after treatment with prednisolone (5 mg/d) and TwHF (20 mg/d), the condition was well controlled, indicating certain efficacy of this combination therapy.

AIDS/HIV

AIDS is an immune deficiency disease caused by HIV infection. Abnormal immune activation is one of the key mechanisms underlying incomplete immune reconstitution in HIV-infected patients receiving regular antiviral therapy (Nakanjako et al., 2011). Suppressing HIV-related abnormal immune activation is crucial for improving patients' quality of life and extending life expectancy.

On one hand, *in vitro* studies have demonstrated that active components of *T. wilfordii* possess anti-HIV properties. Since 1992, several compounds isolated from the plant's roots—including salaspermic acid (Chen, Shi, Kashiwada et al., 1992), tripterifordin (Chen, Shi, Fujioka et al., 1992), neotripterifordin (Chen et al., 1995), triptonine B (Duan et al., 2000), and several sesquiterpene pyridine alkaloids (Horiuch et al., 2006)—have shown anti-HIV replication activity in H9 lymphocytes. Additionally, triptolide and celastrol can directly inhibit HIV replication or transcription by specifically promoting degradation of viral Tat protein (Wan & Chen, 2014) or inducing conformational changes in Tat protein (Narayan et al., 2011). These findings provide support for Tripterygium's anti-HIV effects and suggest its potential for antiviral drug development.

On the other hand, given its potent immunosuppressive effects in RA patients, researchers have investigated whether Tripterygium can suppress HIV-related abnormal immune activation. A clinical trial demonstrated that HIV patients with poor immune response despite combination antiretroviral therapy (cART) showed reduced T-cell activation and significantly increased cluster of differentiation (CD)4 cell counts after 12 months of treatment with TwHF extract (10 mg three times daily) (Li et al., 2015).

Current research on Tripterygium for HIV patients primarily focuses on its application in suppressing abnormal immune activation when combined with antiviral therapy, aiming to increase CD4 cell counts and restore immune response function.

Research Progress in Diabetes and Its Complications

Immunological Abnormalities in the Pathogenesis of Diabetes

Abnormalities in the immune system play a pivotal role in the pathogenesis of diabetes mellitus (Chen et al., 2022). Patients with type 2 diabetes typically exhibit a chronic

low-grade inflammatory state characterized by overactivation of the innate immune system (e.g., macrophage infiltration in adipose tissue), elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), and an imbalance in Th1/Th17 to Treg cell ratios (Jo & Fang, 2021; Jia et al., 2016). This immunometabolic dysregulation creates a vicious cycle by impairing insulin signal transduction and promoting β-cell apoptosis.

Notably, key active components of *T. wilfordii*, particularly celastrol and triptolide, have demonstrated significant efficacy in modulating these pathological processes. Regarding diabetic complications, Tripterygium extracts exhibit distinctive organ-protective effects, primarily manifested through the alleviation of podocyte injury in the kidneys and mitigation of diabetic retinopathy (Fang et al., 2019; Gao et al., 2010; Zhou et al., 2023). These findings provide crucial theoretical foundations for developing Tripterygium-based immunomodulatory therapeutic strategies for diabetes.

TwHF Active Components in Diabetes

The active components of *T. wilfordii* exhibit multi-target and multi-pathway mechanisms in improving diabetes and its complications. Research shows that celastrol can directly bind to carbohydrate response element-binding protein (ChREBP), inhibit its nuclear translocation, and promote proteasomal degradation, thereby downregulating thioredoxin-interacting protein (TXNIP) expression and breaking the vicious cycle between hyperglycemia and TXNIP overexpression (Zhou et al., 2023). Additionally, celastrol promotes glucose consumption by activating the peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α/Glucose transporter type 4 (GLUT4) axis, improves obesity-related metabolic disorders, enhances insulin sensitivity through protein kinase B (AKT) and p38 MAPK signaling pathways, and inhibits hepatic gluconeogenesis via the cyclic-AMP response element binding protein (CREB)/PGC-1α pathway (Fang et al., 2019). These findings collectively reveal celastrol's crucial role in regulating glucose metabolism and insulin resistance, providing a theoretical basis for its potential as a therapeutic agent for type 2 diabetes mellitus (T2DM).

Apart from celastrol, triptolide has also been shown to possess significant anti-diabetic effects. This component primarily reduces the release of inflammatory factors (such as TNF-α and IL-6) by inhibiting NF-κB and MAPK signaling pathways, thereby alleviating inflammation-mediated suppression of insulin signaling. Further studies have found that triptolide can improve obesity-related metabolic abnormalities by regulating T cell subsets (such as increasing CD4+ T cells and decreasing CD8+ T cells) (Gao et al., 2010), suggesting its potential value in regulating the immune-metabolic network (shown in Table 1) (Fang et al., 2019; Gao et al., 2010; Zhou et al., 2023).

Interventions for Diabetic Complications

T. wilfordii demonstrates significant therapeutic effects in diabetic nephropathy (DN). Clinical trials have shown that Tripterygium extract combined with angiotensin receptor blockers (ARBs) significantly reduces proteinuria levels in DN patients (Ge et al., 2013; Xiong et al., 2020). In a randomized controlled trial, the Tripterygium group exhibited a 34.3% reduction in 24-h proteinuria after 6 months, significantly superior to the valsartan monotherapy group (Ge et al., 2013). Animal studies further reveal that Tripterygium ameliorates glomerulosclerosis and tubulointerstitial fibrosis by inhibiting Wnt/β-catenin pathway activation, reducing podocyte injury, and downregulating inflammatory factors (Chang et al., 2018; Hao et al., 2014) (e.g., TNF-α, IL-6). A meta-analysis confirmed that triptolide significantly decreases urinary protein, serum creatinine, and blood urea nitrogen levels in DN animal models (Liang et al., 2021).

Beyond nephropathy, Tripterygium's active components also show beneficial effects on diabetes-related cognitive impairment and obesity. Celastrol alleviates learning and memory deficits in diabetic rats by suppressing NF-κB-mediated neuroinflammation and upregulating insulin signaling pathways (phosphatidylinositide 3-kinases (PI3K)/AKT/glycogen synthase kinase 3β (GSK-3β)) (Zhou et al., 2024). In obesity models, celastrol reduces food intake and promotes glucose uptake by modulating the galanin/PGC-1α pathway, while simultaneously inhibiting hepatic gluconeogenesis (Fang et al., 2019) (Figure 1).

Table 1. Mechanisms of Major Active Components in *Tripterygium wilfordii*.

Component	Target/Pathway	Biological Effect	References
Celastrol	ChREBP–TXNIP axis	Suppresses TXNIP transcription, improves insulin sensitivity	Zhou et al. (2023)
	PI3K/Akt pathway	Enhances GLUT4 membrane translocation	Fang et al. (2019)
Triptolide	NF-κB/IL-1β signaling	Reduces pancreatic inflammation, protects β-cells	Gao et al. (2010)

Note: AKT: Protein kinase B; ChREBP: Carbohydrate response element-binding protein; GLUT4: Glucose transporter type 4; IL-1β: Interlukin-1β; NF-κB: Nuclear factor-κB; PI3K: Phosphatidylinositide 3-kinases; TXNIP: Thioredoxin-interacting protein.

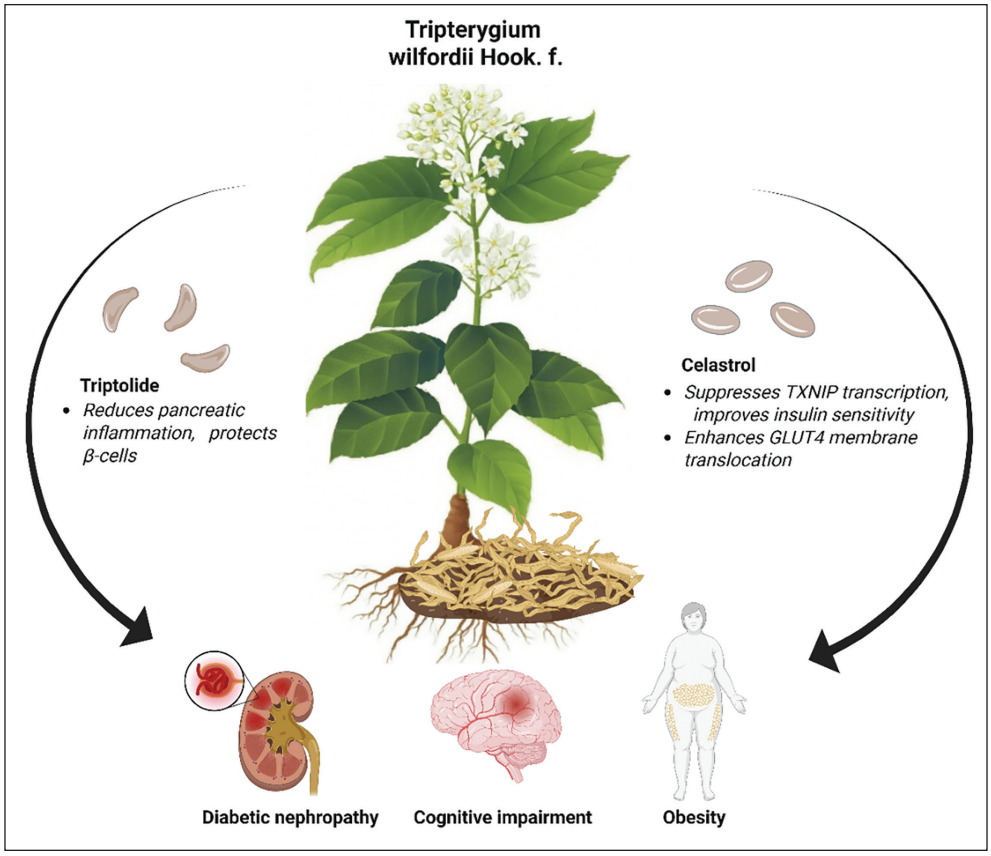


Figure 1. Major Active Components from *Tripterygium wilfordii* in Diabetes Treatment. *Tripterygium wilfordii* Preparations Indirectly Improve Insulin Sensitivity and Glucose Metabolism Through Multiple Pathways, Including Anti-inflammatory Effects, Immune Regulation, Improvement of Lipid Metabolism, and Antioxidant Activity. Thereby, They Mitigate the Damage Caused by Hyperglycemia to the Urinary and Nervous Systems, Help Alleviate Obesity, and Ultimately Slow Down Diabetes-induced Damage to Multiple Organs in the Body.

Safety of Tripterygium Agents

Tripterygium preparations have been studied for the treatment of various diseases due to their potent immunosuppressive effects, with Tripterygium glycosides being widely used in clinical practice. However, both *in vitro* and *in vivo* studies have demonstrated that Tripterygium preparations possess hepatotoxicity (Hasnat et al., 2019; Zhang et al., 2017), nephrotoxicity (Feng, Fang et al., 2019), reproductive toxicity (Guo et al., 2019; Zeng et al., 2017), hematotoxicity, and cardiotoxicity (Fu et al., 2011; Ma et al., 2015), which can cause adverse reactions such as gastrointestinal discomfort (including anorexia and diarrhea), amenorrhea, renal insufficiency, splenomegaly, ovarian atrophy, leukopenia, thrombocytopenia, and aplastic anemia. These adverse reactions may also exhibit gender differences (Liu et al., 2010; Wei et al., 2018). Additionally, case reports have found that Tripterygium treatment can lead to vitamin B12 deficiency (Zhuang et al., 2019), ovarian insufficiency (Yang et al., 2019), as well as cardiogenic shock, bradyarrhythmia, and acute toxic myocarditis (Zhou et al., 2014). The clinical application of Tripterygium preparations is limited by their severe toxicity to multiple organs (Li et al., 2014). Therefore, how to reduce the toxicity while maintaining the therapeutic efficacy of Tripterygium preparations has become a key research focus in their application.

Current research directions to improve the safety of Tripterygium preparations mainly include the following aspects. First, developing Tripterygium derivatives that retain pharmacological activity while exhibiting reduced toxicity. As the main active component, triptolide derivatives represent a breakthrough point, with low solubility, tissue accumulation, and toxicity being the major obstacles in developing triptolide derivatives (Yu et al., 2017). Second, combination therapy or preparation as compound products to maintain the immunosuppressive activity of Tripterygium preparations while reducing toxicity. Research results show that traditional Chinese medicines such as catalpol, Panax notoginseng saponins, *Rehmannia glutinosa*, and *Drynaria fortunei* have synergistic protective effects against triptolide-induced hepatotoxicity (Feng, Fang et al., 2019; Li et al., 2018; Zhang, Li et al., 2018; Zhou, Zhou, Feng et al., 2018), and Tripterygium

preparations processed with certain herbs can reduce toxicity (Wang, Li et al., 2019). Additionally, vitamin C may also play an important protective role in the clinical use of Tripterygium preparations (Xu, Li et al., 2019). Third, using delivery carriers to ensure both efficacy and safety. Nanoparticle loading may improve the circulation time, stability, and biodistribution of triptolide (Ru et al., 2017). Studies indicate that Solid Lipid Nanoparticle (SLN) delivery systems loaded with triptolide can enhance its anti-inflammatory activity while providing protection against its hepatotoxicity (Mei et al., 2005). Fourth, implementing precision medicine to make efficacy and safety predictable. On one hand, as mentioned earlier, more effective treatment approaches can be selected for patients with different symptoms; on the other hand, developing biomarkers to guide optimized treatment regimens, such as circulating miRs that may serve as early warnings for triptolide-induced cardiotoxicity (Wang, Chen et al., 2019), and corticosteroids that may become potential biomarkers for treating multi-organ toxicity caused by triptolide due to its endocrine-disrupting effects (Xu, Wu et al., 2019). Therefore, through scientific treatment protocols and proper patient management, the toxicity of Tripterygium preparations can be effectively avoided, allowing patients to benefit from them.

Discussion

The bioactive components of *T. wilfordii*, particularly celastrol and triptolide, act through mechanisms far beyond the single-pathway approach of conventional glucose-lowering drugs. Their core value lies in simultaneously targeting two central pathological features of type 2 diabetes: insulin sensitivity and chronic low-grade inflammation, thereby enabling multi-target modulation of the immuno-metabolic network.

In improving insulin sensitivity, celastrol enhances insulin sensitivity through the ChREBP–TXNIP axis and promotes glucose transport via the PI3K/AKT pathway. The activation of PI3K/AKT-a core insulin signaling pathway-may not occur in isolation. AKT likely promotes GLUT4 vesicle translocation by phosphorylating and inhibiting AS160. Furthermore, celastrol may modulate AMP-activated protein kinase (AMPK) activity, concurrently enhancing glucose uptake and fatty acid oxidation in skeletal muscle and liver, leading to multi-organ metabolic improvements.

Regarding anti-inflammatory mechanisms, triptolide inhibits the NF-κB and MAPK pathways, blocking the transcriptional burst of key inflammatory cytokines such as TNF-α and IL-6. This potent transcriptional suppression may reprogram macrophages by shifting their polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotype through alterations in key enzymes or metabolites, fundamentally reshaping the immune microenvironment in adipose tissue or pancreatic islets.

Moreover, we propose that these two aspects may interact profoundly at a systemic level. Both celastrol and triptolide effectively suppress inflammatory pathways such as NF-κB and MAPK, alleviating chronic low-grade inflammation and preserving pancreatic β-cell function. Their mechanisms may act synergistically to break the vicious cycle between hyperglycemia and inflammation. However, this cross-pathway synergy remains poorly understood and may be key to their efficacy in ameliorating DN and insulin resistance. Future research must move beyond linear, single-pathway descriptions and adopt systems biology approaches to elucidate crosstalk between these pathways and their tissue-specific regulatory patterns in organs such as adipose tissue, liver, pancreas, and kidneys.

Clinically, Tripterygium extracts show clear benefits. Combined with ARB drugs, they reduce proteinuria in DN better than standard monotherapy. They also show promise in improving diabetes-related cognitive decline and obesity, indicating potential for managing multiple complications. While Tripterygium is unlikely to become a first-line diabetes treatment, it could be a valuable add-on therapy—especially for patients with strong inflammatory responses or early kidney damage who do not respond adequately to conventional drugs.

Despite the benefits of *T. wilfordii* compounds for treating immune and metabolic diseases, their clinical use remains limited by serious side effects that harm the liver, kidneys, heart, and reproductive system. These toxic effects are complex. Some are caused by the drug's intended "on-target" actions (such as transcriptional suppression or key pathway inhibition), while others are "off-target" side effects from the drug spreading to and damaging healthy tissues.

A major goal now is to reduce toxicity focus on structural modification to develop safer derivatives. A compound called (5R)-5-hydroxytriptolide (LLDT-8) is less toxic but still effective. However, its complex synthesis hinders large-scale production, and key aspects-such as its *in vivo* metabolic pathways, major active/toxic metabolites, and potential cumulative toxicity with long-term use—remain poorly understood. Nano-carriers offer a potential solution by improving biodistribution and targeting. Yet, achieving true cell-type-specific delivery (e.g., to renal podocytes or pancreatic β-cells) rather than nonspecific organ accumulation (e.g., in the liver and spleen) remains a major challenge. The biocompatibility of carrier materials, batch consistency in production, and the long-term fate of delivery systems also pose translational barriers. Similarly, although biomarkers such as circulating miRNAs (e.g., miR-146a), inflammatory cytokine profiles, and pharmacogenomic-guided strategies represent ideal tools for personalized therapy, robust predictive models with high sensitivity and specificity-validated in large, multicenter cohorts-are still lacking.

Future research should evaluate whether long-term low-dose regimens can maintain efficacy while reducing chronic toxicity. Studies exploring combination therapy-such as with

sodium-dependent glucose transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists-may reveal synergistic effects. We believe interdisciplinary collaboration is essential to advance this field. This includes using organoids and organ-on-a-chip models to delineate toxicity mechanisms, developing disease-microenvironment-responsive delivery systems, and conducting large-scale prospective real-world evidence studies to ultimately bridge the gap between laboratory research and clinical application of *T. wilfordii*.

Conclusion

T. wilfordii represents a unique class of natural products with potential for treating diabetes and its complications through immunometabolic regulation. Its bioactive compounds and derivatives offer a multi-target, multi-pathway regulatory advantage, demonstrating particular value in improving insulin resistance, suppressing chronic inflammation, and protecting target organs. Clinical evidence supports its significant effect in reducing proteinuria in DN, underscoring its potential as part of a comprehensive diabetes management strategy. Current approaches-such as developing novel derivatives and implementing combination therapy with conventional or herbal agents-have shown promise in mitigating its toxicity. Future research should focus on elucidating its molecular toxicological mechanisms, advancing the clinical translation of less toxic analogs, optimizing individualized dosing regimens, and validating its long-term safety and efficacy in larger-scale diabetes trials.

Abbreviations

AKT: Protein kinase B; ACR20; American College of Rheumatology 20% response; AIDS: Acquired immune deficiency syndrome; AMPK: AMP-activated protein kinase; ARB: Angiotensin receptor blocker; cART: Combination antiretroviral therapy; CCL: Chemotactic cytokines; CD: Cluster of differentiation; ChREBP: Carbohydrate response element-binding protein; CRK: V-crk sarcoma virus CT10 oncogene homolog (avian); CRP: C-reactive protein; CREB: Cyclic-AMP response element binding protein; DMARDs: Disease-modifying anti-rheumatic drugs; DN: Diabetic nephropathy; ESR: Erythrocyte sedimentation rate; GLP-1**:** Glucagon-like peptide-1; GLUT: Glucose transporter; GM-CSF: Granulocyte-macrophage colony stimulating factor; GSK-3β: Glycogen synthase kinase 3β; GRAPL: GRB2-related adapter protein-like; HIV: human immunodeficiency virus; IFN: Interferon; IL: Interleukin; LLDT-8: (5R)-5-hydroxytriptolide; MAPK: Mitogen-activated protein kinase; MCP: Monocyte chemoattractant protein; MIP: Macrophage inflammatory protein; miR: microRNA; MMP: Matrix metalloproteinases; MX1: Myxovirus (influenza virus) resistance 1; NO: nitric oxide; NF-κB: Nuclear factor-κB; NSAIDs: Nonsteroidal anti-inflammatory drugs; OASL: 2′,5′-oligoadenylate synthetase-like; OPG: Osteoprotegerin; PGC: Peroxisome proliferator-activated receptor-gamma coactivator; PGE2: Prostaglandin E2; PI3K: Phosphatidylinositide 3-kinases; RA: Rheumatoid arthritis; RANK: Receptor activator of NF-κB; RANKL: Receptor activator of NF-κB ligand; RNF2: Ring finger protein 2; SHIP: SH2-containing inositol phosphatase; SGLT2: Sodium-dependent glucose transporter 2; sICAM: Soluble intercellular adhesion molecule; SJC: Swollen joint count; SLE: Systemic lupus erythematosus; SOCS: Suppressor of cytokine signaling; SPINK1: Serine peptidase inhibitor Kazal type 1; STAT: Signal transducers and activators of transcription; TJC: Tender joint count; TGF: Transforming growth factor; TIMP: Tissue inhibitors of metalloproteinase; TLR: Toll-like receptor; TNF: Tumor necrosis factor; TwHF: *Tripterygium wilfordii* Hook F.; TXNIP: Thioredoxin-interacting protein; T2DM: Type 2 diabetes mellitus.

Authors' Contributions

Xueyin Wang contributed to data analysis and chart visualization. Yingui Sun contributed to study design, interpretation. Yanwu Jin contributed to funding acquisition. Xueyin Wang drafted the manuscript and gave final approval of the version to be sent.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

Not applicable.

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