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REVIEW

Immunoregulatory effects of *Tripterygium wilfordii* Hook F and its extracts in clinical practice

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Abstract ***Tripterygium wilfordii* Hook F (TwHF) and its extracts have long been used for the treatment of rheumatoid arthritis, autoimmune diseases, and kidney disease due to their anti-inflammatory, immunoregulatory, and other pharmacological effects. However, the clinical immunoregulatory effects of TwHF and its extracts remain unclear, so we reviewed their effects for use in clinical practice. This review provides a comprehensive summary of the recent literature on the immunoregulatory effects of TwHF and its extracts in clinical studies. TwHF and its extracts affect the proliferation and activation of T and B cells; ratio of T cell subsets; inflammatory response of monocytes, macrophages, and immunoglobulins; and secretion of many cytokines. Together, these effects dictate immune function in a variety of diseases. TwHF and its extracts can be used alone or in combination with existing therapies against many immune disorders through immunomodulation.**

Keywords *Tripterygium wilfordii* Hook F; immunoregulation; clinical studies

Introduction

Immunomodulatory disorders include autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Although immunomodulatory compounds, such as corticosteroids and immunosuppressants, have good clinical efficacy, some limitations cannot be ignored, including severe allergic reactions, infections, and anemia. Therefore, identifying safe and effective immunomodulatory drugs with minimal side effects is necessary.

Tripterygium wilfordii Hook F (TwHF) is a wood vine plant that is widely distributed in southern China as a traditional Chinese medicine. TwHF possesses immunoregulatory, anti-inflammatory, anti-tumor, anti-fertility, antibacterial, and other pharmacological properties, and it has been used for the treatment of RA [1], SLE [2], nephritis [3], autoimmune diseases, and allergic skin diseases. Although some patients experience adverse effects with TwHF, including reproductive toxicity, adverse gastrointestinal complications, and hepatotoxicity, reasonable treatment and management strategies can help improve their tolerance for the plant [4]. Tripodine, triptonide, triptolide (TPT), and tripdiolide (TPO) are the main active ingredients of TwHF, and they have been used for many years to treat a range of inflammatory diseases in China with a certain degree of success. Clinical trials have been performed to study the immunomodulatory function of TwHF and its extracts. TwHF can be used as a routine drug for autoimmune diseases and is a highly effective alternative. Although studies have described the immunomodulatory effects of TwHF and its extracts, the molecular mechanisms responsible for these effects are not fully understood. This review aims to further describe the immunoregulatory effects of TwHF in clinical practice.

Immunoregulatory effects of TwHF and their mechanisms of action

The immunoregulatory effects of TwHF mainly target immune cells, immune molecules, and cell signal transduction. Given that T cells are a central part of the immune response, T cell-targeted immune interventions effectively

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control the immunopathology caused by these cells. TwHF exerts multidimensional regulation of T cells. In many autoimmune diseases, abnormalities in $CD4^+$ and $CD8^+$ T cells or an imbalance in Th17 and regulatory T cells (Tregs) can occur. The therapeutic effect of TwHF is related to the regulation of the ratio of $CD4^+$ and $CD8^+$ T cells, the immune balance of Th17 cells and Tregs, and dendritic cell differentiation [5–7]. B cells mainly produce antibodies, present antigens, and secrete cytokines involved in immune regulation and humoral immunity. An alcohol extract of TwHF known as T2 inhibits B lymphocyte proliferation and immunoglobulin production in immune responses [8]. Cytokines are proteins secreted by immune cells that can regulate cell function and the overall immune response. TwHF extracts mainly inhibit the expression of proinflammatory genes such as interleukin (IL)-2, inducible nitric oxide synthase, tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), and interferon (IFN)-γ [9]. Some extracts from TwHF can inhibit the inflammatory response by inhibiting the nuclear factor (NF)-κB signaling pathway [10] and regulating a variety of cytokines, such as the Th1/Th2 cytokine expression profile [11].

Clinical immunoregulatory effects of TwHF

Immune diseases can be caused by the imbalance of immune regulation that affects the body's immune response. Numerous clinical trials have demonstrated the immunoregulatory effects of TwHF. Table 1 and Fig. 1 summarize the molecular targets that mediate the immunoregulatory activities of TwHF and its bioactive components.

Table 1 TwHF and its bioactive components for their targets involved in clinical immunoregulation

Bioactive components	Disease	Action	References	Study design
TWP	RA	Serum TNF-α, IL-6↓	[13,14]	RCT, RCT
	RA	Serum IL-1, TNF-α↓	[15]	Non-RCT
	RA	Serum IL-10, sICAM-1↓	[16]	RCT
	RA	Serum IL-1, IL-6, IL-8, TNF-α, Th1 cell ratio↓, Treg cell ratio↑	[17]	RCT
	RA	Serum CCL5↓	[23]	Non-RCT
	GO	Serum TNF-α, IL-2, IFN-γ↓, IL-10↑	[27]	RCT
	AAU	Serum IL-2, TNF-α↓	[29]	RCT
	CD	$Foxp3^+$ Tregs, IL-10↑, TNF-α↓ from intestinal mucosa	[30]	Before–after study
	CD	Serum TNF-α, IL-1β↓	[31]	Prospective study
	Asthma	$CD4^+$ T cell ratio↓, $CD8^+$ T cell ratio↑	[33]	RCT
	Asthma	Serum IL-2, IL-4, IL-5↓	[34]	Before–after study
	Asthma	IL-5, sIL-2R↓, eosinophil apoptotic rate↑ from sputum	[35]	RCT
	Asthma	IL-4, sIL-2R, sCD23, BRA↓, IFN-γ↑ from PBMCs	[36]	RCT
	GBS	Serum IL-6, CSF IL-6, sIL-2R, Syn IgG↓	[37, 38]	RCT, RCT
	IT	T lymphocyte subpopulations such as CD2, CD4, CD8↓ and normalized the ratio of CD4/CD8	[39]	Non-RCT
	AS	Serum IL-17, PGE2, and MMP-3↓	[40]	Case-control study
	AS	$CD4^+CD25^+CD127^{low}$ Tregs↑, IL-17↓ in blood	[41]	Case-control study
	Psoriasis	Serum IL-6, IL-17, IL-23↓	[42]	Before–after study
	LN	Serum IL-18↓	[45]	Before–after study
	DKD	MCP-1↓ in urine	[46]	Non-RCT
	DKD	TNF-α, $CD4^+$, $CD4^+/CD8^+$↓ in blood	[48]	RCT
	RNS	IL-2, TNF-α, IL-13, IL-6, IL-4↓ in blood	[49]	RCT
TPO	RA	Serum NOB, NETs↓	[22]	Case-control study
TPT	Asthma	IL-2, IL-4, IL-5↓ from PBMCs	[34]	Before–after study
TwHF	SLE	NF-κB↓	[44]	Case–control study
	DKD	CTGF, TGF-β1↓ in urine	[47]	RCT
	CGN	TNF-α, IL-6↓ in blood	[50]	RCT

TWP, *Tripterygium wilfordii* polyglycoside; TPO, tripdiolide; TPT, triptolide; RA, rheumatoid arthritis; GO, Graves' ophthalmopathy; AAU, acute anterior uveitis; CD, Crohn's disease; GBS, Guillain-Barre syndrome; IT, islet transplantation; AS, ankylosing spondylitis; LN, lupus nephritis; DKD, diabetic kidney disease; RNS, recurrent nephrotic syndrome; SLE, systemic lupus erythematosus; CGN, chronic glomerulonephritis; sICAM-1, soluble intercellular adhesion molecule-1; BRA, basophil releasability; PBMCs, peripheral blood mononuclear cells; CSF, cerebrospinal fluid; sIL-2R, soluble interleukin-2 receptor; NOB, neutrophil oxidative burst; NETs, neutrophil extracellular traps; CCL, chemokine (C-C motif) ligand; PGE, prostaglandin E; MMP, matrix metalloproteinase; MCP-1, monocyte chemotactic protein-1; CTGF, connective tissue growth factor; TGF, transforming growth factor; and RCT, randomized clinical trial.

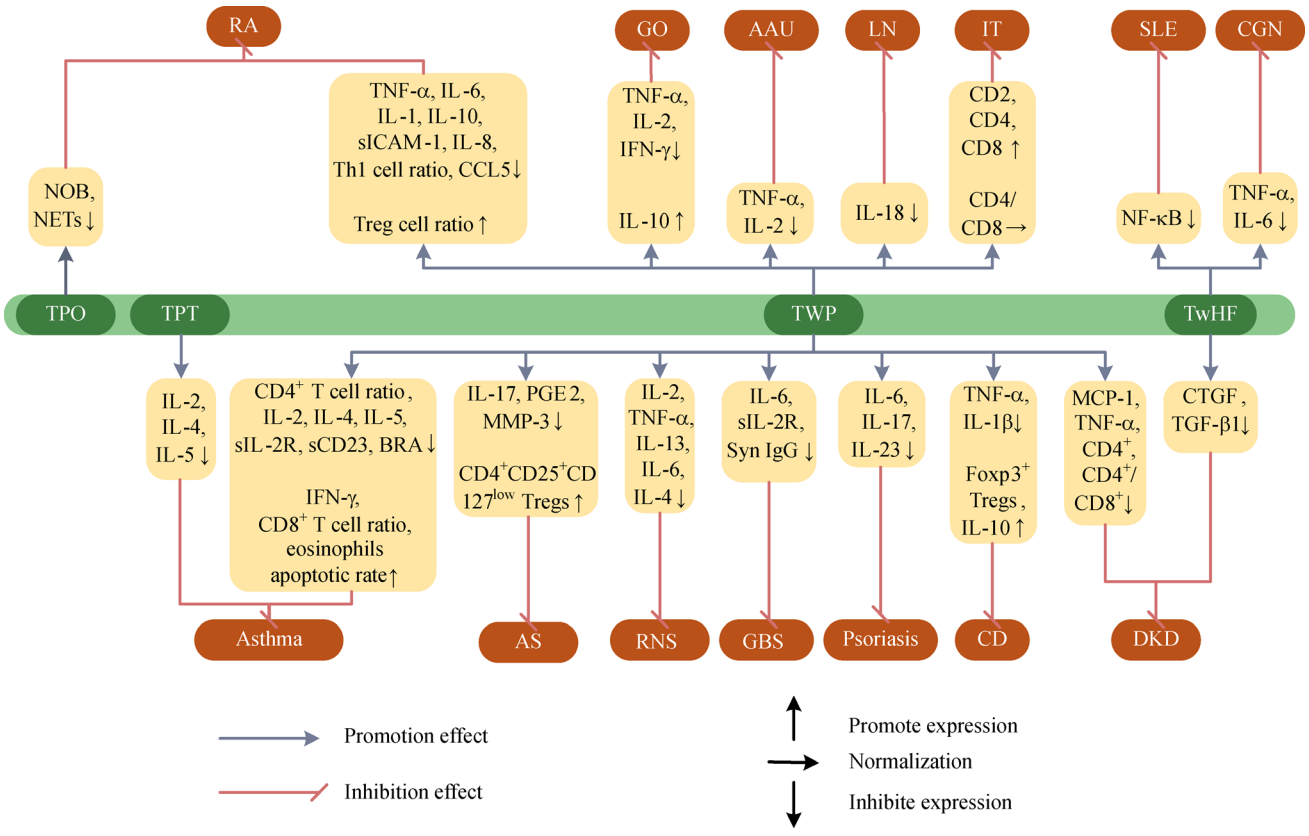

Fig. 1 Immunoregulatory effects of TwHF and its bioactive components for their targets involved in clinical use.

TwHF immunoregulation in RA

RA is a chronic, systemic inflammatory disease associated with swollen joints, pain, and related dysfunction. Clinical and experimental studies have shown that sustained-release TwHF has significant anti-inflammatory, analgesic, and immunosuppressive effects and significantly reduced toxic effects [12]. *Tripterygium wilfordii* polyglycoside (TWP) inhibits the immune response at multiple levels by reducing the serum levels of TNF-α, IL-6, and other cytokines in the treatment of RA [13,14]. Treatment with TWP and leflunomide reduces the serum levels of IL-1, IL-6, IL-10, TNF-α and soluble intercellular adhesion molecule-1 (sICAM-1) in patients with RA, and the changes in IL-1, TNF-α, IL-10, and sICAM-1 are significantly reduced compared with those of the monotherapy group, demonstrating the enhanced anti-inflammatory effects of combined treatment [15,16]. TWP combined with tocilizumab demonstrates obvious clinical efficacy in the treatment of RA, with significantly reduced serum levels of IL-1, IL-6, IL-8, and TNF-α; decreased Th1 cell ratio; and increased Treg cell ratio compared with tocilizumab alone [17]. The regulation of Th1 and Th2 cytokine secretion may be one of the mechanisms by which TWP improves the inflammatory injury of RA.

TwHF not only regulates Th1 and Th2 cytokines but also has varying degrees of impact on other cytokines. TPT is the main active monomer of TwHF in the treatment of RA. Synovial fibroblasts (SFs) treated with TPT were cocultured with $CD4^+$ T cells from healthy volunteers, and TPT was found to inhibit COX-2 level by downregulating prostaglandin E (PGE) 2 secreted by SFs, thereby inhibiting Th17 cell differentiation [18]. Meanwhile, miR-155 can promote inflammatory cell recruitment to aggravate RA synovial inflammation [19]. TPT also inhibits the expression of TNF-α, IL-6, and miR-155 in peripheral blood mononuclear cells (PBMCs) of patients with RA stimulated by lipopolysaccharide, whereas the overexpression of miR-155 significantly reverses the inhibition of proinflammatory cytokine expression. Moreover, TPT upregulates the suppressor of cytokine signaling-1 (SOCS1) and SH2-inositol phosphatase 1 (SHIP-1) expression in PBMCs of patients, whereas the overexpression of miR-155 reverses the upregulation of SHIP-1 without affecting SOCS1 expression [20]. TPT treatment reduces the activation of matrix metalloproteinase (MMP)-9 and the TNF-α-induced expression of phosphorylated c-Jun N-terminal kinases, which may also explain the therapeutic effects of TPT on the aggressive behavior of RA SFs [21].

Neutrophil extracellular traps (NETs) play a pivotal role in autoimmune diseases with inflammation-mediated organ damage. TPO, one of the main active components in TwHF, completely inhibits neutrophil oxidative burst and NET formation induced by the IgG purified from sera of a patient with RA via downregulation of the spleen tyrosine kinase-mitogen-activated protein kinase kinase-extracellular-signal-regulated kinase-NF-κB signaling cascade, further providing a potential mechanism for the decrease in autoantibody production in RA [22]. Besides, chemokine (C–C motif) ligand (CCL) 5 plays an important role in RA and is overproduced in RA bone marrow, which may contribute to the accumulation of T cells observed in RA bone marrow. TWP treatment can reduce the level of CCL5 in patients with RA [23].

TwHF immunoregulation in immune thrombocytopenia (ITP)

ITP is an autoimmune hemorrhagic disease with many immune dysfunctions, including a low percentage of $CD4^+$ T cells and a high percentage of $CD8^+$ T cells [24]. Multigly-TwHF combined with recombinant human IL-11 (rhIL-11) increases the ratio of $CD4^+$ T cells in peripheral blood from 21.03% to 34.49% after 2 months of treatment for ITP. Thereafter, the ratio of $CD8^+$ T cells in the peripheral blood decreases from 26.35% to 20.18%. Multigly-TwHF can also correct T cell dysfunction and shorten the treatment period when combined with rhIL-11. With few side effects, this combination may be safe and effective for the treatment of ITP [25].

TwHF immunoregulation in ophthalmology diseases

Graves' ophthalmopathy (GO) is an organ-specific autoimmune disease associated with the elevation of multiple serum Th1 cytokines (including TNF-α, IL-2, and IFN-γ) [26]. The levels of TNF-α, IL-2, and IFN-γ in peripheral blood significantly decrease in patients with moderate to severe acute GO treated with TWP, whereas the concentration of IL-10 significantly increases compared with that of prednisone, with a total clinical efficacy of 88.10% for the treatment group [27]. *In vitro*, TPT can inhibit the IFN-γ-induced activation of cultured retro-ocular fibroblasts derived from patients with GO [28]. In addition, TWP can significantly inhibit the levels of IL-2 and TNF-α in patients with acute anterior uveitis (AAU), thereby providing a reliable therapeutic effect on AAU [29].

TwHF immunoregulation in Crohn's disease (CD)

Tregs expressing Forkhead box P3 (Foxp3) play an important role in maintaining intestinal homeostasis by secreting IL-10 and transforming growth factor (TGF)-β. Many studies have found a correlation between $Foxp3^+$ Tregs and CD. TWP has been shown to be clinically effective in inducing CD remission due to the relief of the pathological inflammation of CD. Specifically, the levels of $Foxp3^+$ Tregs and IL-10 in the mucosa of patients with CD significantly increase, whereas TNF-α is downregulated after TWP treatment [30]. TWP may exert a therapeutic effect on mildly or moderately active CD by reducing the serum levels of TNF-α and IL-1β [31].

TwHF immunoregulation in myasthenia gravis (MG)

MG is a rare autoimmune disease associated with failure of neuromuscular transmission. In the treatment of MG, TWP combined with prednisone can significantly reduce serum IL-6 and peripheral blood B lymphocyte levels compared with prednisone alone [32]. In addition, TWP with prednisone is superior to prednisone alone in the treatment of MG and exhibits a strong immunosuppressive effect [32].

TwHF immunoregulation in asthma

The balance between the Th1 and Th2 responses maintains normal cellular and humoral immunity. In the treatment of patients with asthma, TWP reduces the ratio of $CD4^+$ T cells and increases the ratio of $CD8^+$ T cells for regulating the balance between T lymphocyte subsets [33]. This treatment also reduces the serum levels of IL-2, IL-4, and IL-5 [34]. TPT also reduces the abovementioned cytokines secreted by the PBMCs of patients [34].

After TWP treatment, sputum IL-5 and soluble interleukin-2 receptor (sIL-2R) significantly decrease [35]. In addition, IL-4, sIL-2R, and sCD23 in the supernatants of PBMCs from patients with asthma are significantly lower than those in the control group, whereas the IFN-γ content significantly increases [36]. The inhibition of T and B cell activation, correction of the Th1 and Th2 cytokine imbalance, and reduction in basophil releasability may be some of the important mechanisms for the anti-inflammatory and anti-asthmatic effects of TWP [35,36].

TwHF immunoregulation in Guillain–Barre syndrome (GBS)

The biological function of IL-6 is to promote B lymphocyte proliferation and differentiation, which is necessary to produce antibodies. sIL-2R provides an important signal to the immune system for cellular activation. In GBS treatment, TWP inhibits the immune response to adrenal corticosteroid abnormalities, and the clinical improvement rate and levels of IL-6, sIL-2R, and Syn IgG are significantly better with TWP treatment compared with hormone therapy [37,38]. Thus, TWP inhibits the abnormal immune response in patients with GBS better than hormones.

TwHF immunoregulation in islet transplantation (IT)

IT is an important therapeutic mean to cure insulin-dependent diabetes mellitus (IDDM), but immune tolerance is crucial for long-term efficacy after transplantation. In patients with IT, TWP inhibits the number and function of T lymphocyte subsets such as CD2, CD4, and CD8 and normalizes the $CD4^+/CD8^+$ ratio. TWP also prolongs the survival time of patients with IT and IDDM by inhibiting immune rejection [39].

TwHF immunoregulation in ankylosing spondylitis (AS)

IL-17 is also an inflammatory cytokine that is closely correlated with erythrocyte sedimentation rate and C-reactive protein levels contributing to the development of AS. In the treatment of AS, TWP exerts an anti-inflammatory effect by regulating the levels of IL-17, PGE2, and MMP-3 [40]. Tregs can suppress immune reaction, and their absence in the blood of patients with AS may contribute to the pathogenesis of AS. The ratio of $CD4^+CD25^+CD127^{low}$ Tregs in patients with AS significantly increases after TWP treatment. TWP is efficient for the treatment of patients with AS, and its mechanism of action may be correlated with the upregulation of $CD4^+CD25^+CD127^{low}$ Tregs and the downregulation of IL-17 in the peripheral blood [41].

TwHF immunoregulation in psoriasis

Psoriasis is a chronic relapsing inflammatory skin disease involving a variety of immune cells, factors, and inflammatory mediators. Aside from lowering the psoriasis area and severity index in patients with psoriasis vulgaris, TWP treatment for 8 weeks can reduce the serum levels of IL-6, IL-17, and IL-23 [42]. These results also explain that TWP can regulate Th17 lymphocyte immune function in the treatment of psoriasis.

TwHF immunoregulation in human immunodeficiency virus (HIV)

Immune activation plays a crucial role in 20% of patients infected with HIV who are unable to achieve adequate immunologic recovery. TwHF extract has immunomodulatory effects that may help CD4 cell recovery. In the treatment of patients with HIV via combined antiretroviral therapy, the use of TwHF extract is correlated with reduced T cell immune activation and CD4 cell recovery [43].

TwHF immunoregulation in SLE

After treatment with TwHF, NF-κB activity in patients with SLE significantly decreases, reaching a level similar to that in patients with inactive SLE. The pathogenesis of SLE is complex, and TwHF may inhibit the expression of NF-κB to exert its immunosuppressive effect on SLE [44].

TwHF immunoregulation in nephropathy

IL-18 is a cytokine with multiple biological functions. TWP inhibits the production of plasma IL-18 to control lupus nephritis activity [45]. TWP treatment can improve the renal function and reduce proteinuria in patients with diabetic kidney disease (DKD), which is caused by reduced urinary excretion of monocyte chemotactic protein-1 to inhibit the inflammatory response [46]. The pro-inflammatory factors of connective tissue growth factor (CTGF) and TGF-β1 are associated with DKD pathogenesis and contribute to podocyte impairment. TwHF treatment can prevent DKD development by reducing the urinary levels of CTGF and TGF-β1 [47]. TWP can also improve the immunity imbalance of patients with DKD by inhibiting the expression of $CD4^+$, $CD4^+/CD8^+$, and TNF-α [48].

In addition, TWP may have a therapeutic effect in children with recurrent nephrotic syndrome, which is closely related to the reduction in cytokine levels of IL-2, TNF-α, IL-13, IL-6, and IL-4 from Th1 and Th2 in peripheral blood [49]. TNF-α is an inflammatory mediator produced by activated mononuclear cells and macrophages that stimulate glomerular cells, neutrophils, and vascular endothelial cells, and its levels are elevated in patients with chronic glomerulonephritis (CGN). IL-6 is an important inflammatory cytokine that plays a role in the immune pathogenesis of CGN and glomerular sclerosis. TwHF treatment can reduce the expression of TNF-α, IL-6, and other inflammatory cytokines, indicating that it regulates the balance of cell-mediated immunity and humoral immunity to inhibit inflammatory reactions. Therefore, the therapeutic effect of TwHF on kidney function and improvement in clinical symptoms are related to its inhibition of the expression of TNF-α and IL-6 [50].

Conclusions

The immunomodulatory and anti-inflammatory properties of TwHF make it an attractive drug for the treatment of autoimmune diseases. Combining TwHF with other drugs or altering the use of ingredients or methods may reduce its adverse effects. TwHF and its extracts exert a regulatory effect on immune function by regulating the proliferation and activation of T and B cells, proportion of T cell subsets, inflammatory response of monocyte and macrophage, production of immunoglobulin and a variety of cytokines, and other complex mechanisms. However, the molecular mechanisms responsible for these effects need to be studied further, including the signaling pathways of cells

and molecules. The immunosuppressive effects of this compound mainly focus on TWP, and the immune promotion of TwHF has not been considered. Formulations with minimal side effects and the identification of the precise immunomodulatory functions of TwHF should be determined prior to use in clinical applications. Further studies on the immunoregulatory effects of TwHF and its extracts may explain their function and modes of action, and TwHF has great potential as an effective immunomodulatory drug.

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Compliance with ethics guidelines

Dan Luo, Zhengyun Zuo, Hongyan Zhao, Yong Tan, and Cheng Xiao declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

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