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REVIEW

Tripterygium wilfordii Hook. F. and Its Extracts for Psoriasis: Efficacy and Mechanism

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Abstract: Psoriasis is an inflammatory autoimmune skin condition that is clinically marked by chronic erythema and scaling. The traditional Chinese herb *Tripterygium wilfordii Hook. F.* (TwHF) is commonly used in the treatment of immune-related skin illnesses, such as psoriasis. In clinical studies, PASI (Psoriasis Area and Severity Index) were dramatically decreased by TwHF and its extracts. Their benefits for psoriasis also include relief from psoriasis symptoms such as itching, dryness, overall lesion scores and quality of life. And the pathological mechanisms include anti-inflammation, immunomodulation and potentially signaling pathway modulations, which are achieved by modulating type-3 inflammatory cytokines including IL-22, IL-23, and IL-17 as well as immune cells like Th17 lymphocytes, γδT cells, and interfering with IFN-SOCS1, NF-κB and IL- 36α signaling pathways. TwHF and its extracts may cause various adverse drug reactions, such as gastrointestinal responses, aberrant hepatocytes, reproductive issues, and liver function impairment, but at adequate doses, they are regarded as an alternative therapy for the treatment of psoriasis. In this review, the effectiveness and mechanisms of TwHF and its extracts in psoriasis treatment are elucidated.

Keywords: efficacy, mode of action, *Tripterygium wilfordii Hook. F.*, psoriasis, type-3 inflammation

Introduction

Introduction of Psoriasis

Psoriasis is an inflammatory immune-mediated skin condition characterized by chronic widespread papules, scales, and erythema. It is more prevalent in high-income countries, with frequency ranging from 0.1% in East Asia to 1.5% in Western Europe.[1] Approximately 120 million individuals are affected globally.[2] The severity of the illness is assessed using PASI (Psoriasis Area and Severity Index), which takes into consideration the presence of erythema, scaling, thickness, infiltration, and the extent of the lesions.[3] Different clinical phenotypes of psoriasis exist, however, persistent plaque or psoriasis vulgaris is the most common and most easily recognized.[1] Psoriasis is an autoimmune disease that affects the innate and adaptive immune systems, with KCs (keratinocytes), T lymphocytes, and DCs (dendritic cells) playing important roles.[4] Both environmental and genetic factors, such as smoking, can influence the clinical progression of psoriasis.[5,6] (Figure 1) Originally, psoriasis was thought to be caused by a disorder of epidermal keratinocytes.[7] Subsequent research has shown that Th1 cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-12 (IL-12) play an important role in the development of psoriasis.[8] Recent studies have also revealed that psoriasis is characterized by immunological abnormalities in Th17 cells and Th17 cytokines such as IL-17A and IL-17F, so as known as type-3 inflammation, as well as abnormal keratinocyte differentiation and proliferation.[9,10] Furthermore, the IL-23/Th17 pathway/axis takes a critical role in the etiology of psoriasis.[11–13] Patients with psoriasis have a much higher risk of depression and suicide, according to studies.[14,15] Therefore, finding an effective treatment for psoriasis is essential to lessening the severe effects of the condition on one's physical, social, and psychological well-being. Currently, traditional psoriasis therapies include the topical application of drugs including corticosteroids, vitamin D3

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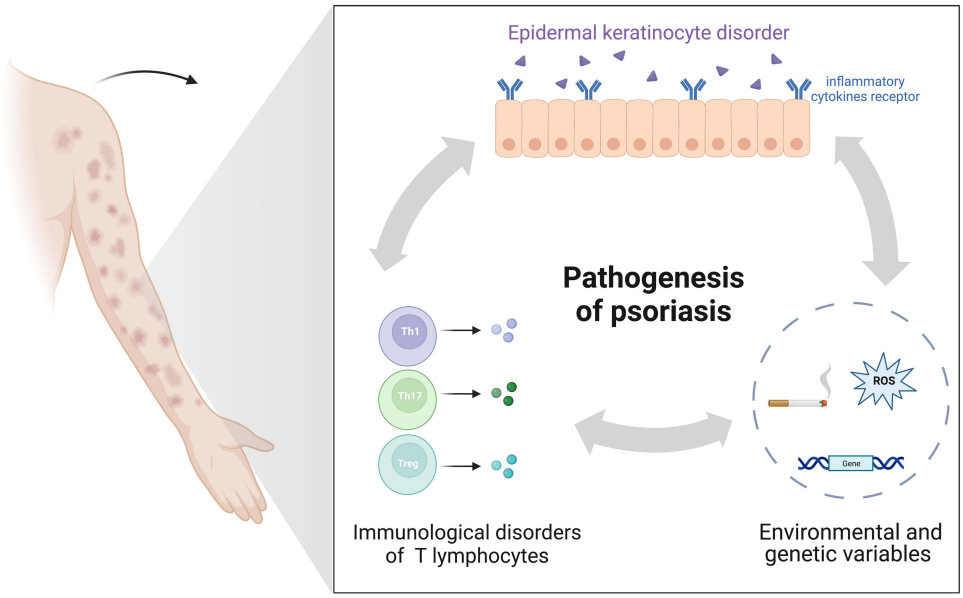

Figure 1 The pathogenesis of psoriasis.

analogues, calcineurin inhibitors, keratolytics, and combination topical medication, as well as systemic medications like methotrexate (MTX), apremilast, ciclosporin, and acitretin.[1] Over the last 20 years, monoclonal biologics have been successfully approved for psoriasis treatment targeting highly specific cytokines like TNF-α, IL-12, IL-17, and IL-23, which have higher efficacy than chemical drugs. Physical therapy and topical medicines are recommended for those with mild to severe psoriasis. Systemic medicine and monoclonal biologics are suitable for moderate to severe psoriasis.[16] There are still limitations in the systemic treatment of psoriasis. For example, Acitretin, a retinoid used to treat psoriasis, is associated with dose-dependent pneumonia as the most common side effect, along with other adverse effects such as eye problems, liver inflammation, and teratogenicity, particularly contraindicated in women of childbearing age, and may also cause minor side effects like dose-dependent hair loss and dry skin.[2,17] At the same time, MTX, a frequently employed primary systemic therapy for psoriasis, exhibits teratogenicity and potential adverse effects, including the risk of hepatotoxicity, myelosuppression, and other detrimental reactions, potentially resulting in liver cirrhosis. Therefore, long-term, vigilant monitoring of hepatic function and hematological parameters is imperative.[1,18] Moreover, the limitations of monoclonal biologics include a much greater expense than some other psoriasis therapies and there is still a not insignificant percentage of patients who do not respond to the drug at all.[19] Therefore, the current selection of pharmacological treatments for psoriasis is not satisfactory for medical needs due to its recurrent lengthy course, high recurrence rate, and low efficiency of psoriasis treatment.[20] And there may be potential benefits in developing traditional medicines, particularly novel traditional medicines as a form of therapy. To mitigate the profound impact of psoriasis on an individual's physical, social, and psychological well-being, there is a compelling need for further research into novel medications that can efficiently address the condition, all the while offering enhanced affordability and safety compared to current treatment options.

Introduction of Compounds in the Treatment of Psoriasis

Chinese Herbal Medicine, owing to its rich repository of potentially bioactive compounds, has found extensive application in the management of autoimmune disorders such as psoriasis, rheumatoid arthritis, and ulcerative colitis. This widespread usage can be attributed to the relatively extensive safety profile and multifaceted therapeutic benefits it offers.[21] It globally recognized as promising drug candidates for the treatment of a broad spectrum of chronic diseases due to their sustained safety profile, even during extended usage, and the high level of patient compliance they engender.[22]

A considerable amount of evidence on the efficacy and safety of Chinese Herbal Medicine has already been established through previous studies.[23] Notably, resveratrol, prevalent in red grapes and wine, exhibits antioxidative

and anti-inflammatory attributes.[24] Curcumin, derived from turmeric, is renowned for its potent anti-inflammatory and antioxidant effects, often necessitating strategies to enhance its bioavailability.[25] Boswellic acids, obtained from Boswellia serrata, hold promise for their anti-inflammatory potential.[25] Epigallocatechin gallate (EGCG), extracted from green tea, offers antioxidant and anti-inflammatory properties.[26] Triptolide, derived from the Thunder God Vine, presents potent anti-inflammatory and immunosuppressive actions, which accompanied by complex ADME characteristics, including concerns regarding toxicity.[27] Indirubin, a traditional Chinese medicine component, has been recognized for its anti-inflammatory benefits.[28] Olibanum, sourced from Boswellia trees, has demonstrated anti-inflammatory and immune-modulating effects.[29] Phytocannabinoids, found in cannabis, exhibit anti-inflammatory and immune-modulating properties and its ADME properties are contingent on specific compounds and consumption methods.[21] Licorice, containing glycyrrhizin, showcases anti-inflammatory and immune-modulating effects.[30] Quercetin, a flavonoid distributed across diverse plants, demonstrates antioxidant and anti-inflammatory attributes.[31] Aloe-emodin, present in plants such as aloe vera, exhibits laxative and anti-inflammatory characteristics which ADME profiles are influenced by source and preparation.[32] These compounds present a promising avenue for further research into effective psoriasis treatments and these ADME variations underscore the necessity for tailored approaches and therapeutic strategies, while their unique properties underscore the need for tailored approaches and therapeutic strategies in clinical practice. (Table 1) In particular, *Tripterygium wilfordii Hook. F.* has been used for centuries to relieve symptoms of immune-mediated inflammatory disease such as RA (rheumatoid arthritis), SLE (systemic lupus erythematosus), psoriasis, ankylosing spondylitis, and idiopathic IgA nephropathy, as well as cancer treatment.[33–35]

Introduction of *Tripterygium wilfordii Hook. F.* and Its Application

Tripterygium wilfordii Hook. F. (TwHF) is a vine plant belonging to the genus Tripterygium of the Celastraceae family that is also known as "Lei Gong Teng", "Thunder God Vine" and "Huang Teng", and it has a long history of cultivation mainly in southern China.[38] It was initially featured as a cure for several types of arthritis in Mao Lan's book "Dian Nan Ben Cao" in 1476.[39] TwHF

Table 1 Material Basis of Compounds in the Treatment of Psoriasis

Compound	Sources	Formula	Bioactivity	Anti-Psoriatic of Mechanism	Reference
Resveratrol	Vitis vinifera, Polygonum cuspidatum	C14H12O3	Antioxidant, cardioprotection, chemoprevention, anti-inflammation	Inhibit inflammation, reduce pro-inflammatory immune mediators	[24]
Curcumin	Curcuma longa	C21H20O6	Antioxidant, anti-inflammation, antibacterial, antiviral activity	Ameliorate lesion by reducing T cell proliferation and production of cytokines	[25]
Boswellic Acids	Boswellia	C32H48O5	Anti-inflammation, anti-arthritic, anti-cancer activity	Changes in scales and extent of erythema at the site of lesions with a topical application	[29]
Epigallocatechin-3-gallate (EGCG)	Camellia sinensis	C22H18O11	Anti-cancer, anti-inflammation, inhibition of oxidative stress-induced protein tyrosine nitration, improvement of mitochondrial function	Ameliorate psoriasis lesion	[26]
Triptolide	TwHF	C20H24O6	Anti-inflammation, immunomodulation, signaling pathway regulation, anti-tumor, neurotrophic, neuroprotective	Inhibit inflammation, reduce PASI	[27]
Indirubin	Indigofera tinctoria L	C16H10N2O2	Anti-inflammation, anti-tumor, promotion of interferon-β production, regulation of MAVS signaling	Anti-proliferative, regulatory differentiation	[36]
Frankincense	Boswellia serrata	C7H13NO4	Anti-inflammation, antimicrobial activity, antioxidant, aromatherapy	Reduces PASI, psoriasis lesions, and inflammatory factors	[37]
Phytocannabinoids	Rhododendron species and liverworts	C21H30O2	Pain modulation, anti-inflammatory effects, anti-anxiety properties, antiemetic (preventing nausea and vomiting), immune system modulation	Regulate immune cell function, inhibit excessive inflammatory response and reduce oxidative stress	[21]
Licorice	Glycyrrhiza glabra	C42H62O16	Anti-inflammation, anti-viral, immune-modulation, potential benefits for digestive health.	Anti-inflammation and immune-modulating properties	[30]
Quercetin	Apples, onions, and capers	C15H10O7	Antioxidant, anti-inflammation	Anti-inflammation, immunomodulation,	[31]
Aloe-emodin	Rheum palmatumL	C15H10O5	Anti-cancer, antioxidant, antibacterial activity	Alleviate skin inflammation and itching	[32]

contains over 400 natural products that have been isolated and characterized, including sesquiterpenes, diterpenes, triterpenes, lignans, glycosides, and alkaloids.[38] Among these compounds, triptolide (diterpene) and celastrol (triterpene) are the most biologically active and promising.[40] (Figure 2) TwHF tablets and TwHF multiglycoside tablets have been used as a traditional Chinese medicine to treat rheumatoid arthritis symptoms since the 1970s.[41–44] The woody root of TwHF contains the majority of the traditionally and legally used medicinal ingredients and is recommended by Chinese dermatologists for the treatment of psoriasis.[45] Subsequent studies have revealed that TwHF and its extract possess significant beneficial pharmacological activity, including anti-inflammatory,[46,47] immunosuppressive,[48,49] antineoplastic,[50,51] and antiangiogenic[52] properties, so that they have been approved in China for treating autoimmune and inflammatory diseases such as RA and SLE.[35,53] Their pharmacological mechanisms and effects have been extensively studied in the treatment of immune-related disorders including RA, SLE, ankylosing spondylitis, and various skin diseases including psoriasis.[38,40,43] The negative effects of TwHF and its extracts, on the other hand, have severely limited their potential clinical applicability in the treatment of disorders, and identifying the right treatment plan is critical.[54] This suggests that TwHF may be applicable to all immune-mediated inflammatory diseases, and the shift in therapeutic strategy in recent years from broad-spectrum immunomodulators to the use of highly specific targeted agents suggests that tight control of inflammation is critical to disease outcome.[55] Even though the exact causes of psoriasis are still unknown, it is known that a number of pathways connected to inflammation have a role in the pathogenesis. Given this, it becomes sense to assume that TwHF's underlying mechanism involves a multicomponent, multi-targeted action that modifies the immune system and the systemic inflammatory state linked to the symptoms of psoriasis.[23]

TwHF and its extracts have been commonly used in psoriasis treatment in recent years, with the use of TwHF and its extracts for the treatment of psoriasis has gained popularity in recent years, with Triptolide and celastrol serving as the primary active ingredients. While there have been reports on the effectiveness of TwHF and its extracts in treating psoriasis, this review aims to provide a concise overview of the clinical efficacy, mechanism, and safety of TwHF and its extracts in treating psoriasis, in order to emphasize its potential for clinical use. The review will provide a useful reference for relevant research and contribute to the ongoing development and clinical use of TwHF by summarizing the effectiveness and mechanisms of TwHF and its extracts. Therefore, this review is essential for serving as a reference point for pertinent research, advancing the progress and clinical application of TwHF and its extracts.

Efficacy of Tripterygium in Psoriasis Treatment

Clinical Trial and Case Report

Several clinical studies have demonstrated the efficacy of TwHF and its extracts in treating psoriasis. A clinical comparative study including 91 subjects evaluated the tolerability of a new emollient balm containing celastrol whether topically used alone or in combination with topical or systemic medication therapies or phototherapy. The researchers discovered that using a celastrol-containing emollient balm for topical treatment on the entire body once a day can help with psoriasis symptoms including itching, dryness, and global lesion scores and the quality of patients' life is improved, according to the patient-reported outcome questionnaire. In conclusion, it is crucial to assure long-term compliance that patients with psoriasis vulgaris tolerate this novel emollient cream containing celastrol effectively, whether used alone or in conjunction with medication or phototherapy. Pruritus, symptoms, and quality of life are improved after one month of daily usage.[56] For the systemic treatment of TwHF, the results of a small simple prospective randomized clinical trial (RCT), enrolling 115 moderate to severe

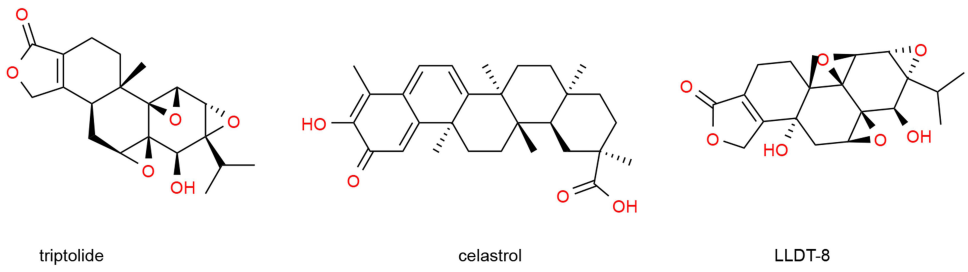

Figure 2 Structural formula of chemical components isolated from *Tripterygium wilfordii Hook. F.*

psoriasis vulgaris patients (PASI score ≥10 and body surface area afflicted by psoriasis ≥ 10%), show no significant difference in treatment effectiveness between the TwHF group (20 mg, 3 times a day) and acitretin group (20 mg, 3 times a day) within 8 weeks, however, the TwHF group had fewer treatment-related side events. This suggests that Tripterygium wilfordii Hook F. may be an efficient and secure therapy for people with moderate to severe psoriasis vulgaris, while its usage may be constrained by side effects such menstruation abnormalities.[57] What's more, in another randomized controlled trial conducted by Fu et al, it was found that the combination of tripterygium wilfordii glycoside (TWGs) tablets and acitretin was more effective and safer in treating moderate to severe plaque psoriasis (MSPP). 36 MSPP patients were collected and separated into three groups: group A (12 patients received TWG tablets plus acitretin capsules), group B (12 patients received compound glycyrrhizin capsules plus acitretin capsules), and group C (12 patients received acitretin capsules). In terms of serum parameters, clinical effectiveness, PASI score, and incidence of adverse events, group A's therapeutic impact were clearly superior to that of the other two groups.[58] As such, these studies show that TwHF and its extracts positively affect treating psoriasis (Table 2).

In addition, not only clinical trials but also many case reports have shown significant efficacy of TwHF psoriasis treatment. In a retrospective analysis including 26 patients with generalized pustular psoriasis in southwest China, 11 among them were effective with TwHF.[59] An open clinical and one-year-follow study enrolling 103 patients with psoriasis vulgaris evaluated the effect and safety of triptolide tablets with a PASI score, and the results proved an overall efficacy rate of 75% in 103 patients. In addition, only 5 patients experienced adverse effects.[60]

Systematic Review

Recently, researchers have conducted multiple clinical trials to evaluate the efficacy of TwHF and its extracts in treating psoriasis. They can be used alone or in combination with systemic medications like acitretin. Han et al evaluated ten randomized or quasi-randomized clinical controlled studies of TwHF extracts with psoriasis patients, in which the efficacy of existing authorized psoriasis medicines was compared by using TwHF extracts alone or in combination with them. The results of the meta-analysis of these ten clinical studies showed a statistically significant improvement in psoriasis following therapy with TwHF extract, demonstrating that TwHF has a beneficial effect on plaque, pustular, and erythrodermic psoriasis types.[61] Another meta-analysis and systematic review including 20 randomized controlled studies with 1872 psoriasis vulgaris evaluated the clinical effectiveness and safety of TwHF in psoriasis treatment. The results revealed that despite the mild adverse effects of TwHF, it reduces the Psoriasis Area Severity Index (PASI) scores of patients and remains effective in the treatment of psoriasis. It is evident that TwHF can clearly improve overall efficacy in the treatment of psoriasis vulgaris when used in conjunction with other medication therapies, whether herbal tonics or western pharmaceuticals.[62]

Outcome and Prospect

In establishing diagnostic criteria for psoriasis in clinical trials, the choice is made in accordance with the specific clinical indications of the drug under consideration. For instance, in the case of topically applied creams containing celastrol, Thouvenin et al opted for patients exhibiting stable mild-to-moderate body plaque psoriasis lasting for over 6 months, with a PASI score of less than 10 and a pruritus intensity of at least 3 on a Numerical Rating Scale. On the other hand, in randomized controlled trials comparing Tripterygium wilfordii Hook F to Acitretin, researchers, such as Wu et al, focused on patients with moderate to severe psoriasis vulgaris, with inclusion criteria based on a PASI score greater than or equal to 10 or a psoriasis-affected body surface area of 10% or more. Meanwhile, Fu et al included adults with a PASI score ranging from 7 to 20 points. It is noteworthy that nearly all studies excluded patients who had received drug treatment and topical medication for skin lesions within the preceding 6 months to ensure control over relevant variables. Above all, the positive effects of TwHF and its extracts in the treatment of psoriasis, including a significant decrease in PASI and a relief from psoriasis symptoms such as itching, dryness, overall lesion scores and quality of life, suggest that they could be an alternative as a therapeutic drug for psoriasis.

Table 2 Clinical Trial of TwHF and Its Extracts on Psoriasis

Medicine	Dosage	Type of Psoriasis	Subject	Study Design	Criteria	Outcome	Length	Treatment Result	P-value	Reference
Celastrol	Apply over the whole body once a day	Psoriasis vulgaris	91 subjects (41 celastrol balm only and 50 celastrol balm with systemic treatment) with celastrol	Randomized, double-blind, controlled, intrapatient trial	Patients with body plaque psoriasis. Aged 18–70 years. Exclusion criteria: severe plaque psoriasis (not responding to the treatment for the study of the balm in association), erythrodermic psoriasis, pustular psoriasis, palmoplantar keratoderma, a history of hypersensitivity or intolerance to any cosmetic product, and women whose oral contraception was initiated or changed within the previous 3 months.	Pruritus, symptoms, and quality of life are improved after one month of daily usage	4 weeks	Mean pruritus intensity score decreased 39% at day 8 and 60% at day 29 compared with day 1, the body global lesion score decreased 24% at day 8 and 26% at day 29	P < 0.001	[56]
Tripterygium wilfordii Hook F	20mg, 3 times a day	Moderate to severe psoriasis vulgaris	115 subjects (58 TwHF and 57 acitretin) with TwHF	Randomized, double-blind, double-dummy, parallel-group clinical trial	Adults with moderate to severe psoriasis vulgaris. Aged 18–75 years. PASI≧10 or psoriasis-affected body surface area 10% or higher. Exclusion criteria included: psoriatic erythroderma, psoriasis pustulosa, psoriasis arthritis, or guttate psoriasis; taking systemic corticoid, immunosuppressive agents, or biologicals therapy during the past 4 weeks; taking local corticoid therapy or phototherapy during the past 2 weeks; patients that are pregnant, breastfeeding, planning to become pregnant within 2 years.	TwHF and acitretin demonstrated similar treatment efficacy, with fewer treatment-related adverse events in the TwHF group.	8 weeks	The median PASI score improved by 50.4±31.0%, PASI score decreased from a median of 23.8 (range 7.5–59.5) to 11.1 (range 0.3–46.9)	P < 0.0001	[57]
Tripterygium Wilfordii Glycoside Tablets (TWG)	3 times a day	Moderate to severe psoriasis vulgaris (MSPP)	36 subjects (12 TWG tablets + acitretin capsules, 12 compound glycyrrhizin capsules + acitretin capsules and 12 acitretin capsules alone) with TWG tablets	Randomized, controlled, intrapatient trial	Patients diagnosed as MSPP by clinical examination; aged over 18 years old. Signed an informed consent for this study; with seven points < PASI score < 20 points; without drug treatment and topical medication for skin lesions within 6 months; exclusion criteria: suffered from severe hepatic and kidney function damage, cardiovascular disease, and autoimmune diseases; had coagulation dysfunction; diagnosed with allergic diseases; had malignant tumors; in either pregnancy or lactation period; contraindicated or withdrawn during the administration.	TWGs combined with acitretin had better therapeutic effects and higher safety	8 weeks	TWGs have superior satisfactory results of serum parameters, clinical efficacy and PASI score, and incidence of adverse reactions to the other two groups.	P < 0.05	[58]

The Mechanism of Action

The primary pharmacological effects of TwHF are anti-inflammatory and immune regulation. Notably, the compounds celastrol and triptolide derived from TwHF exhibit efficacy against conditions characterized by inflammation, such as RA.[63] These compounds target various signaling pathways, including NF-κB, endoplasmic reticulum Ca2+-ATPase, myeloid differentiation factor 2, toll-like receptor 4, pro-inflammatory chemokines, DNA damage, cell cycle arrest, apoptosis, receptor activator of NF-κB (RANK)/RANK ligand/osteoprotegerin, cyclooxygenase-2, matrix metalloproteases, and cytokines. These actions contribute to immune response modulation, which is frequently overactive in psoriasis. Additionally, TwHF can regulate signal pathways involved in both the inflammatory response and immune system function, helping to restore balance to the overactive immune response observed in psoriasis. In summary, aside from its well-known anti-inflammatory and immune regulatory functions, TwHF also possesses mechanisms for repairing damage. This summarizes the targets and signaling pathways associated with TwHF and its formulations in the treatment of psoriasis (Table 3 and Figure 3).

Effect of *Tripterygium wilfordii Hook. F.* on Inflammation

Psoriasis development is closely associated with inflammation, where abnormally activated skin dendritic cells secreting IL-23 and TNF-α.[77] High levels of pro-inflammatory cytokines such as IL-1, IFN, IL-12, IL-17, IL-22, and IL-23 will interact with keratinocytes, leading to possible hyperproliferation and activation.[78] In addition, activated keratinocytes release proinflammatory cytokines, chemokines, and antimicrobial peptides in inflamed skin, recruiting and triggering immune cells.[79] TwHF and its extracts can eliminate inflammation and consequently regulate inflammatory factors.

HaCaT cells, immortalized human KCs, exhibiting similar features to KCs in psoriasis, such as excessive proliferation and aberrant differentiation. Triptolide, for example, reduces the proliferation of HaCaT cells (immortalized human keratinocytes) triggered by IL-22 and promotes KC differentiation by upregulating miR-181b-5p, implying that triptolide might be a possible psoriasis treatment.[65] Several studies have investigated the use of carriers for celastrol, such as encapsulation of celastrol by niosomes, to enhance its therapeutic efficacy in treating psoriasis. These studies have consistently demonstrated the significant effectiveness of celastrol in reducing erythema and scaling in imiquimod-induced psoriasis mouse models and in decreasing the levels of inflammatory cytokines like TNF-α, IL-6, IL-22, IL-23, and IL-17 in HaCaT cells.[67–69] Additionally, Tripterygium wilfordii poly-glycosides (TWP), extracted from *Tripterygium wilfordii Hook. f.*, have been shown to possess anti-inflammatory and immunosuppressive effects. TWP suppressed HaCaT cell proliferation and production of inflammatory cytokines by lowering the ratio of neutrophil elastase to Trappin-2 levels, offering a novel insight into TWP's anti-psoriasis mechanism.[73] In conclusion, TwHF and its extracts can reduce the degree of inflammation in psoriasis by modulating inflammatory cytokines such as TNF-α, IL-6, IL-22, IL-23, and IL-17.

Effect of *Tripterygium wilfordii Hook. F.* on Immunomodulation

Psoriasis is an immune-related skin disease, in which the abnormal immune function of Th17 and Treg as well as their cytokines, play an essential part in the pathogenetic mechanism.[11] The importance of the IL-23/Th17 axis in psoriasis pathophysiology has been proven in recent clinical trials and investigations. The paradigm of cytokine research has evolved from Th1 to Th17, with IL-17 and IL-22 serving as Th17 cytokines in psoriasis patients to activate and stimulate the proliferation of KCs.[80–83] TwHF and its extracts have the capacity for immune modulation through interacting with relevant immune cells, cytokines, and chemokines.

TwHF and its extracts have been shown to have a beneficial modulatory impact on immunomodulation in psoriasis in several investigations. According to a study, in keratinocytes, celastrol enriched extract (CEE) inhibits both Th17 and Th22 differentiation and factors stimulated by IL-17, IL-22, and IFN-α, thereby lowering the levels of Th17/Th22 cytokines such as IL-19, IL-23, IL-36c, CCL5, CCL20, CXCL1, and IL-8, which are major inflammatory parameters, and key biomarkers associated with psoriasis, implying that CEE could be used as adjuvant therapy for psoriasis.[71] In mice with imiquimod-induced psoriasis-like dermatitis, celastrol gel was shown to decrease the release of IL-23 from Langerhans cells, downregulate the connection between Langerhans cells and γδ T cells, and decrease the number of

Table 3 Pharmacological Mechanisms of TwHF and Its Extracts on Psoriasis

Drug	Molecular Formula	IUPAC	Function	Target	Model	Study Detail	Outcome of the Study	Reference
LDTT-8	C20H24O7	(1S,2S,4S,5S,7R,8R,9S,11S,13R)-8,13-dihydroxy-1-methyl-7-propan-2-yl-3,6,10,16-tetraoxaheptacyclo	Signaling pathway regulation	IL-36α pathway	BALB/c mice treated with 62.5 mg IMQ cream on back for seven days	20,50 μg/kg/day for 7 days	Suppressing the IL-36α signaling pathway	[64]
Triptolide	C20H24O6	(1S,2S,4S,5S,7R,8R,9S,11S,13S)-8-hydroxy-1-methyl-7-propan-2-yl-3,6,10,16-tetraoxaheptacyclo	Anti-inflammation	miR-181b-5p	HeCaT Cells transfected with miR-181b-5p antagomir for 24 hours	10μM Triptolide for 24 h	Inhibiting the Proliferation of HaCaT cells	[65]
			Signaling pathway regulation	JAK/STAT pathway	HeCaT Cells stimulated with 500 U/mL recombinant human interferon-gamma (rhIFN-γ)	Triptolide at concentrations ranging from 10–10 to 10-8 M	Inhibiting IFN-γ signaling pathway	[66]
Celastrol	C29H38O4	(2R,4aS,6aR,6aS,14aS,14bR)-10-hydroxy-2,4a,6a,6a,9,14a-hexamethyl-11-oxo-1,3,4,5,6,13,14,14b-octahydropicene-2-carboxylic acid	Anti-inflammation	DCs	C57/BL mice treated with IMQ cream (62.5 mg containing 3.125 mg of the active ingredient) on back for 6 days	CEL-loaded mannose-modified liposomes (CEL-MAN-LPs) at a concentration of 375 ug/kg/day	Enhancing uptake and anti-maturation effect on dendritic cells	[67]
				KCs	C57/BL mice treated with IMQ cream (3.125 mg of the active ingredient) on back for 7 days; HaCaT cells	Celastrol Niosome hydrogel at a dosage of 0.08 mg/day	Inhibiting the inflammation and hyperproliferation of keratinocytes	[68]
				IL-17, IL-23p40, IL-γ, IL-22	C57BL/6 mice treated with 3 mg IMQ cream on back for five days	Celastrol at a dose of 4mg/kg/day	Improving the anti-psoriasis activity	[69]
			Immunomodulation	IL-23 secreted by LCs; IL-17 secreted by γδT cells	C57BL/6 and Langerin-DTR mice treated with 15.6 mg IMQ cream on ears for five days	Celastrol gel at a concentration of 0.008%,0.02%.0.06% for seven days	Ameliorating imiquimod-induced psoriasis-like dermatitis in mice by targeting Langerhans cells	[70]
				Th17/Th22 pathway	Hcd4, NHEK, RAE	Celastrol enriched extract (CEE) at concentrations of 3, 10, 30 and 90 ng/mL	Inhibiting Th17/Th22 pathway	[71]
			Signaling pathway regulation	NF-κB pathway; BCL-2 family	HaCaT cells	Celastrol at concentrations of 0.55/1.1/2.2 Um for24hours	Inhibiting NF-κB activity	[72]
Tripterygium wilfordii polycoride	C20H24O6	–	Anti-inflammation	The balance of neutrophil elastase and trappin-2	HaCaT cells	TWP (Tripterygium wilfo r dii polycoride) at a concentration of 50 ug/mL	Reducing the proliferation and inflammatory cytokines secretion of HaCat cells	[73]
			Immunomodulation	Th17 through the inhibition of STAT3 phosphorylation	BALB/c mice treated with 42 mg of 5% IMQ cream on back for eight days	GTW (Multi-glycoside of Tripterygium wilfordii Hook. F.) at a dose of 10, 20 and 40 mg/kg/day	Ameliorating imiquimod-induced skin lesions	[74]
			Signaling pathway regulation	IL-17 signaling pathway and Th17 cell differentiation.	BALB/c with 62.5 mg/d 5% IMQ on the shaved back (2 × 3 cm)	10 mg/kg/d (TWP-L), 20 mg/kg/d (TWP-M) and 40 mg/kg/d (TWP-H) Tripterygium wilfordii polyglycosides (TWP) were respectively used in TWP treatment groups	Ameliorating skin lesions, decreasing inflammatory response and inhibiting the differentiation of Th1/Th17 cells	[75]
TwHF root decoction (TwHF-RD)	–	–	Immunomodulation	Bcl-2, caspase-8/caspase-3 apoptosis pathways; Th-17 cell	BALB/c mice treated with 10mg/cm² IMQ cream on back for five days	TwHF-RD at a dose of 0.04,0.08,0.2,0.4 or 0.8 mg/cm²/day	Alleviating IMQ-induced psoriasis lesions and apoptosis of KC and immune cells	[76]

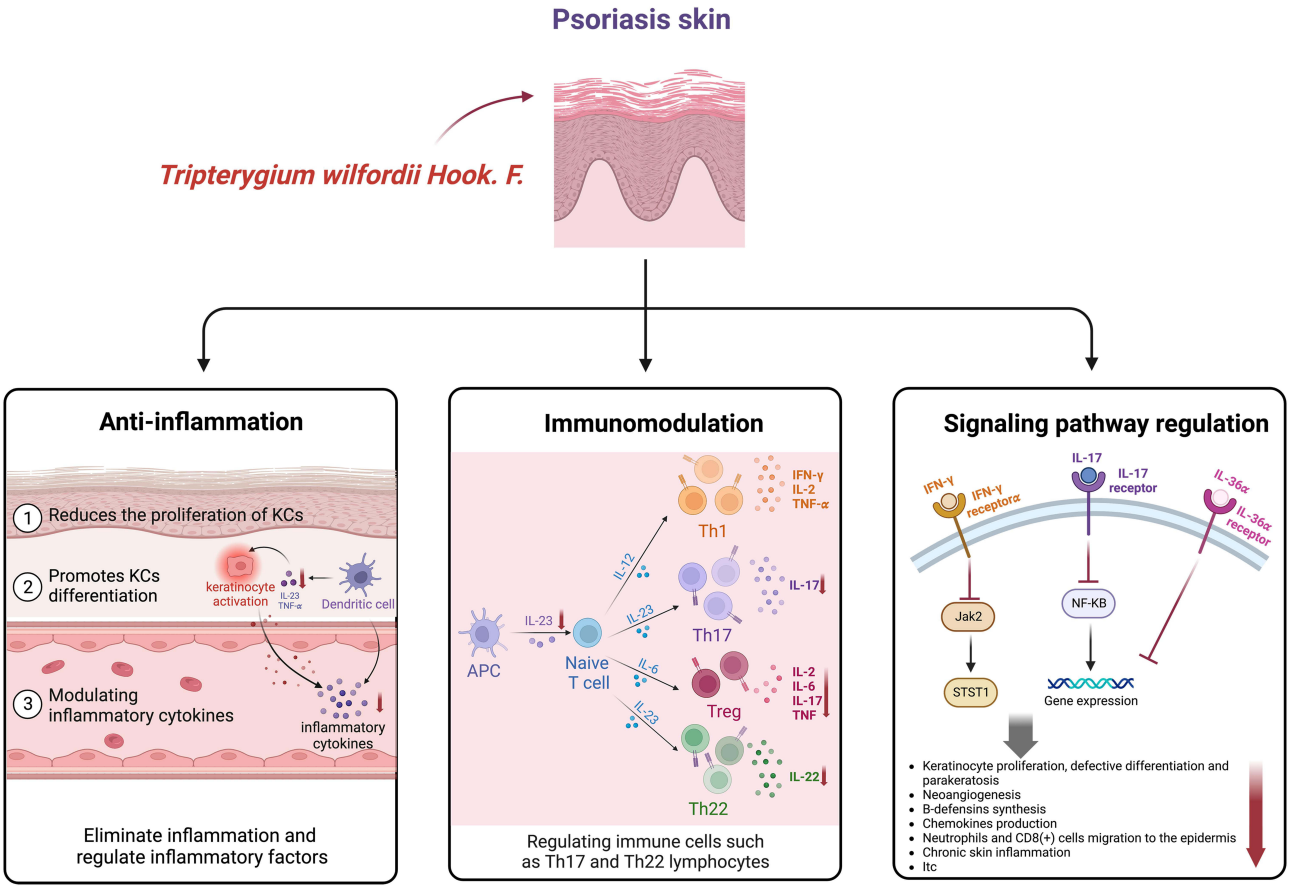

Figure 3 Pharmacological mechanisms of TwHF and its extracts on psoriasis.

T cells that are stimulated and the concomitant IL-17 production. It ameliorates psoriasis-like dermatitis and also has a glucocorticoid-like effect, which successfully prevents psoriasis recurrence.[70] Another study demonstrated that GTW (multi-glycoside of *Tripterygium wilfordii Hook. f.*) reduced the level of inflammation in lesions developing psoriasis in mice after topical IMQ administration, which was linked to substantially lower mRNA levels of Th17 cytokines like IL-17A, IL-17F, and IL-22 as well as a reduction of IL-17-secreting CD4+ immune cells in the spleen of IMQ-exposed mice.[74] Ru et al found that TwHF root decoction (TwHF-RD) could attenuate psoriatic lesions induced by IMQ through modulating KC proliferation and apoptosis, inhibiting the differentiation of T cells and Treg, and reducing the expression of pro-inflammatory cytokines.[76] Overall, immune function plays a key role in the occurrence of psoriasis, whereas TwHF and its extracts have the function of immunomodulation by regulating immune cells such as Th17 and Th22 lymphocytes and γδ T cells.

Effect of *Tripterygium wilfordii Hook. F.* on Potential Signaling Pathway Regulation

The pathology of psoriasis is complex and dynamic, and the mechanisms through which TwHF exerts its therapeutic effects remain unclear. Recent studies have focused on investigating the specific pathways, cytokines, chemokines, and targets that TwHF acts on in psoriasis. It has been suggested that TWP could be able to treat psoriasis by inhibiting the IL-17 signaling pathway and the differentiation of Th17 cells, which may be common therapeutic methods. TWP effectively improves skin lesions, lessens inflammation, and prevents the differentiation of Th1/Th17 cells, according to animal research. The effects of TWP on MAPK14, IL-2, and IL-6 were discovered using molecular docking and qPCR confirmation. TWP also inhibits the growth of Th17 cells and the IL-17 signaling pathway. However, it has also been found that TWP has potential hepatotoxic effects, revealing 145 hepatotoxic targets, including ALB, CASP3, and HSP90AA1, which are associated with the development of Th17 cells and the IL-17 signaling cascade.[75] Triptolide, a component of TwHF, has been shown to disrupt the IFN-γ

signaling pathway by suppressing the expression of IFN-γ receptor α (IFN-γRα), the activation of Jak2 (Janus kinase 2), and STAT1 (signal transducer and activator of transcription 1), and up-regulating the expression of SOCS1 (suppressor of cytokine signaling 1). This suggests that triptolide acts directly on skin cells (KCs) and thus plays an anti-inflammatory role, which further supports the therapeutic value of TwHF in treating IFN-γ-dependent skin inflammatory illnesses like psoriasis.[66] Celastrol, another component of TwHF, has been linked to inducing apoptosis in HaCaT cells, through death receptor and mitochondrial pathways, as well as the suppression of the NF-κB pathway.[72] Another study found that a safer triptolide derivative LLDT-8 ((5R)-5-hydroxytriptolide) could reduce the expression of IL-36α and block IL-36α signaling, notably alleviating psoriasis-like skin inflammation in IMQ-induced mice through inhibiting the IL-36α signaling pathway.[64] Above importantly, these findings provide new insights into the mechanisms underlying the therapeutic effects of TwHF in psoriasis and suggest potential targets for psoriasis treatment.

The studies cited above provide evidence that the therapeutic effects of TwHF and its extracts in treating psoriasis can be attributed to their anti-inflammation, immunomodulation, and potentially signaling pathway modulatory functions, which are achieved by modulating inflammatory cytokines such as IL-22, IL-23, IL-17 and immune cells such as Th17 lymphocytes, γδT cells and interfering with IFN-SOCS1, NF-κB and IL- 36α signaling pathways.

Adverse Effects

Even though TwHF and its extracts have been proven effective in treating psoriasis, their potential side effects should be carefully considered. Han et al reported that gastrointestinal complaints, aberrant hepatocytes, and reproductive dysfunction are the most common side effects of TwHF extracts.[61] A meta-analysis of 14 studies revealed TwHF-related toxicity in systemic application, including menstrual disorders in women, dry mouth, gastrointestinal complaints, swelling of the lower limbs, abnormal hepatocytes, and abnormal routine blood results.[62] Another meta-analysis reveals that TwHF may also cause higher reproductive toxicity, severe skin responses, hematologic problems, and cardiovascular events.[84] TwHF-related adverse effects are systemic, and organ-specific, and are associated with factors such as dosing schedule, co-interventions, and medication dosage.[54,85] In addition, large dosages of TwHF may cause significant side effects such as cardiac shock and renal failure[86] (Table 4).

Table 4 Adverse Effects of Celastrol, Triptolide and TwHF in Psoriasis Treatment

Medication	Adverse Drug Reaction	Frequency	Common Symptoms	Management
Celastrol	Hepatotoxicity	High	Liver injury, oxidative stress	Monitor liver function, dose adjustment
	Nephrotoxicity	High	Renal damage, oxidative stress	Monitor kidney function, hydration, potential dose adjustment
	Cardiotoxicity	Variable	Inhibition of hERG channel activity, potential cardiac issues	Monitor cardiac function, dose adjustment
	Ototoxicity	Variable	Hearing loss, inner ear cell apoptosis	Monitor auditory function
Triptolide	Hepatotoxicity	High	Severe liver injury, oxidative stress	Monitor liver function, dose adjustment
	Nephrotoxicity	High	Renal damage, oxidative stress, nephrotoxicity	Monitor kidney function, hydration, potential dose adjustment
	Hematological effects	Variable	Hematological abnormalities, leukopenia	Regular blood tests, potential dose adjustment
	Reproductive toxicity	Variable	Impact on fertility, spermatogenesis issues	Strict contraception for men and women of childbearing age
TwHF	Gastrointestinal Issues	Common	Nausea, vomiting, diarrhea	Symptomatic relief, dose adjustment
	Nephrotoxicity	Variable	Renal damage, oxidative stress	Monitor kidney function, hydration, potential dose adjustment
	Neurological Effects	Variable	Headaches, dizziness	Monitoring and symptomatic treatment
	Reproductive Toxicity	Variable	Impact on fertility, spermatogenesis issues	Strict contraception for men and women of childbearing age

In comprehensive examination of TwHF and its extracts, we have meticulously elucidated the complex landscape of its toxicity profile, specifically focusing on organ systems. Hepatotoxicity is a well-documented adverse effect of TwHF. It can cause liver injury, often marked by elevated liver enzymes and oxidative stress. Metabolomic analysis revealed that the hydroxyl group at C-14 in the molecular structure of triptolide is associated with hepatotoxicity. Triptolide-induced liver toxicity occurs in a dose- and time-dependent manner and is characterized by apoptosis. Triptolide and celastrol induced hepatotoxicity by reducing the substrate affinity, activity and expression of cytochrome P450 (CYP450) at the transcriptional and protein levels which related to PI3K/AKT, MAPK, TNFα and p53 signal pathways.[87–89] Moreover, TwHF can induce renal damage characterized by injured renal tubules and oxidative stress, which damage proximal tubules and affect the tight junction complex and paracellular permeability. It is mediated by the GSK-3β/Fyn pathway and leads to degradation of Nrf2 and renal tubular cell apoptosis.[90,91] Additionally, TwHF can induce gastrointestinal symptoms, including nausea, vomiting and diarrhea, hematological abnormalities, and potential bone density issues, necessitating in-depth exploration of mechanisms and clinical implications.[61] Cardiotoxicity as well as adverse reproductive effects, are also notable findings.[92–94] Importantly, potential drug interactions, which may impact treatment outcomes, should be a point of clinical consideration (Table 5).

In conclusion, despite the efficacy of TwHF and its extracts in treating psoriasis, there exist potential adverse effects, mainly including gastrointestinal reactions, hepatic impairment, reproductive problems, hepatic impairment, skin adverse reactions, cardiovascular events, and renal failure. Because the toxicity of TwHF shows a correlation with the dose, it is critical to prescribe a safe dose to minimize adverse effects.

Conclusion and Future Perspective

This article presents a review of current scientific research on the composition, clinical efficacy, and mechanism of action of TwHF in the treatment of psoriasis. Although the therapeutic potential of TwHF in the treatment of psoriasis has been previously investigated, this review specifically focuses on the latest developments in TwHF research, with the aim of providing a comprehensive understanding of the mechanisms underlying TwHF's effectiveness in treating psoriasis and informing future clinical investigations.

The pathogenesis of psoriasis has not been fully studied so far, and the present treatment of psoriasis is primarily with western drugs, such as methotrexate and acitretin, and biologics, including Adalimumab and Etanercept, but they must be

Table 5 Summary of Toxicity Findings of TwHF and Its Extracts

Organ/ System Studied	Findings	Mechanisms	Reference
Liver	Hepatotoxicity, oxidative stress	Metabolic alterations, pathways affected	[87–89]
Kidney	Nephrotoxicity, oxidative stress	Upregulate the expression of tubular injury markers such as kidney injury molecule-1 (KIM-1) and gelatinase-associated lipocalin (NGAL) in the kidney, disruption of cell–cell junctions and alterations in paracellular permeability in the proximal tubule	[90,91]
Cardiovascular	Cardiotoxicity	Inhibit hERG channel activity in human embryonic kidney 293 cells and GLUT1 and GLUT4 expression	[95,96]
Gastrointestinal	Gastrointestinal issues, symptoms like vomiting, diarrhoea, leukopenia, renal failure, profound hypotension and shock after oral administration of the extract	-	[61]
Ear	Ototoxicity	Suppress the cell proliferation and viability of inner ear stem cells.	[92]
Reproductive system	Fertility issues	Impact on spermatogenesis, ovarian toxicity, by decreasing the expression of spermatogenesis-related genes, including spe-10, spe-15, fer-1 and folt-1 and promotes granulosa cell apoptosis	[93,94]

closely monitored for adverse reactions and increase the financial burden of patients due to the long-term and repeated recurrence of psoriasis. A large number of studies have shown that TwHF and its extracts have positive efficacy on psoriasis with fewer side effects, and their pharmacological effects such as anti-inflammation, immunomodulation, and potential signaling pathway modulation have been widely and deeply understood and studied.

TwHF and its extracts have demonstrated some efficacy in the treatment of psoriasis, although they are not without adverse effects. Many clinical investigations have identified gastrointestinal responses, aberrant hepatocytes, reproductive issues, hepatic impairment, cutaneous adverse reactions, cardiovascular events, and renal failure as side effects of TwHF and its extracts. Hepatic impairment is the most prevalent of these problems. As a result, unfavorable responses to TwHF and its extracts during clinical application should be taken seriously, which limits TwHF's widespread usage. However, there is some evidence of clinical efficacy of TwHF from the clinical trials, but high quality randomized double-blind placebo-controlled studies are missing. From the data presented it may be concluded that TwHF extracts might be preferably used topically to avoid systemic side effects.

Although TwHF and its extracts have been utilized for treating psoriasis, there remain several issues that need to be resolved. First, comprises several active components, necessitating systematic inheritance, development, and innovative studies on their dose-related toxicity, efficacy, and mechanisms of action to achieve safe and effective clinical application and improve social and economic benefits. Second, TwHF and its extracts are typically administered orally or topically in clinical psoriasis treatment. To better exploit TwHF's clinical benefits and lay the groundwork for its further theoretical clinical implementation, a novel drug delivery mechanism that overcomes TwHF's physical and chemical limitations should be investigated. Lastly, the existing pharmacodynamic studies of TwHF and its extracts lack a thorough explanation of the structure, function, and guiding principles of its active components, focusing mainly on skin damage treatment effectiveness. It should be investigated at the cellular and molecular levels, and future research should focus on its pharmacokinetics and metabolites.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. N-N.D. was responsible for its financial supports and the corresponding works.

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