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Review:

Use of *Tripterygium wilfordii* Hook F for immune-mediated inflammatory diseases: progress and future prospects*

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Abstract: *Tripterygium wilfordii* Hook F has significant anti-inflammatory and immunosuppressive properties and is widely used for treating autoimmune and inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and kidney disease, especially in traditional Chinese medicine. The mechanisms underlying its effects may be diverse but they remain unclear, and its toxicity and side effects limit its wider clinical application. This review summarizes the clinical application of *Tripterygium wilfordii* Hook F in recent years, as well as the results of studies into its mechanisms and toxicity, to provide a reference for its future clinical application.

Key words: *Tripterygium wilfordii* Hook F; Anti-inflammation; Immunosuppression
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1 Introduction

Tripterygium wilfordii Hook F (TwHF), a member of the Celastraceae family of vine-like plants, is an important drug in traditional Chinese medicine, first recorded in the 16th-century Compendium of Materia Medica. TwHF has significant anti-inflammatory and immune-modulating properties, and is widely used in various autoimmune-mediated inflammatory diseases, including rheumatoid arthritis, nephrotic syndrome, systemic lupus erythematosus, and Behcet's disease. Traditionally, TwHF was administered as a decoction; however, following extensive research on this drug, its extracts are increasingly used in the clinic. So far, more than 70 chemical components have been isolated, including alkaloids, diterpenoids, triterpenoids, etc., among which triptolide and tripterine are the most active and the most studied extracts (Hu et al., 2013). TwHF has a significant curative effect on autoimmune diseases with no hormone-related side effects, so it has attracted the attention of many researchers over recent years, with many studies investigating the potential mechanisms for its anti-inflammatory and immunosuppressive effects. However, TwHF has known toxicity and side effects, which limits its wider clinical application.

This review summarizes the clinical application of TwHF over recent years for immune-related

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inflammatory diseases, its anti-inflammatory and immunoregulatory mechanisms, and the methods currently used to reduce its toxicity. The aim of the review is to provide a better understanding of the biological characteristics and mechanisms of this drug and to provide a reference for its clinical application and promotion.

2 Clinical application for immune-related inflammatory diseases

2.1 Rheumatoid arthritis

The currently available disease-modifying antirheumatic drugs and biological agents used to ameliorate rheumatoid arthritis, a chronic autoimmune disease, have limited efficacy and are expensive. TwHF, known as "the Chinese herbal hormone," has been recognized as effective for treating the condition. A study that treated rheumatoid arthritis patients with TwHF, methotrexate (MTX), or a combination of both and followed them over a 24-week period, reported that TwHF was as effective as MTX and superior to MTX monotherapy in controlling disease activity, and that the combined treatment significantly increased the curative effect, achieving an effective rate of 76.8% (Lv et al., 2015). Similarly, a meta-analysis of six randomized controlled trials (643 patients) reported that the combination of TwHF and MTX significantly improved the arthritis symptoms and controlled the disease activity of patients with rheumatoid arthritis, with no increase in adverse reactions compared with the single drug treatment schemes (Wang XY et al., 2017). Thus, the combination of TwHF and MTX may be a safe and effective treatment for rheumatoid arthritis. However, there remains a need to explore combinations of TwHF with other drugs.

2.2 Dermatosis

The pathogenesis of many dermatologic diseases is related to autoimmune abnormalities, such as systemic lupus erythematosus, psoriasis, pemphigus, and Behcet's disease. TwHF has been reported to have a definite therapeutic effect on these diseases. A clinical study (Liu et al., 2014) showed that the effective rate of TwHF combined with prednisone for the treatment of systemic lupus erythematosus was 87.5%, significantly higher than the rate for the control (prednisone combined with MTX). In that study, the experimental group showed superior results to the control group for 24-h urine protein, complement component 3 levels, and the systemic lupus erythematosus disease activity index (SLEDAI) score for disease activity. There was a higher incidence of menstrual disorders in the experimental group, but no significant difference between the two groups in other adverse reactions. Liu et al. (2014) concluded that prednisone combined with TwHF was generally superior to prednisone combined with MTX as a treatment for systemic lupus erythematosus. In addition, a meta-analysis has shown that TwHF alone or in combination with other immunosuppressive drugs has a better curative effect for psoriasis vulgaris and lower incidence of adverse reactions (Han et al., 2012; Lv et al., 2018). These findings suggest that the application of TwHF in dermatology has great potential.

2.3 Renal disease

TwHF has good efficacy for a various kidney diseases, including chronic glomerulonephritis, nephrotic syndrome, diabetic nephropathy, and lupus nephritis. Compared with the conventional treatment for diabetic nephropathy, tripterygium glycosides, which are derived from TwHF, can reduce urine protein content and increase the clearance rate of endogenous creatinine, with a clear curative and protective effect on kidney function. Recent clinical studies have shown that tripterygium glycosides combined with irbesartan had a better curative effect for immunoglobulin A (IgA) nephropathy than monotherapy with tripterygium glycosides or irbesartan. The combination of these two drugs showed a better synergistic protective effect on renal podocyte injury than either drug in monotherapy, delaying the progress of the disease (Liang et al., 2019). Refractory nephrotic syndrome is currently treated with hormones and immunosuppressive drugs, but the long-term use of these can result in severe toxic and side effects, and the condition has a high risk of recurrence and poor prognosis. TwHF acts in a similar manner to a hormone but with no hormonal side effects, and it shows good therapeutic effects in refractory nephrotic syndrome. In a study of patients with refractory nephrotic syndrome, Chen et al. (2015) compared tripterygium glycosides in combination with mycophenolate mofetil

to monotherapy with mycophenolate mofetil. A comparison of renal function showed a better curative effect with the combined therapy and a significantly lower recurrence rate, suggesting that the combination of mycophenolate mofetil and tripterygium glycosides may be an effective treatment method for refractory nephrotic syndrome.

2.4 Rejection after organ transplantation

TwHF exerts a strong immunosuppressive effect, so it has been used to protect against the rejection reaction after organ transplantation. Wang et al. (2015) randomly divided 80 prospective kidney transplant recipients into two groups. All received triple immunosuppressive therapy (cyclosporin, mycophenolate mofetil, and hormones), with the experimental group also receiving TwHF. There was no acute rejection reaction after kidney transplantation in the experimental group, compared with a rate of 10% in the control group, and the incidence rate of rejection within six months was 2.5% in the experimental group and 15.0% in the control group (Wang et al., 2015). Other studies have reported that the long-term use of TwHF after kidney transplantation can reduce the incidence of rejection and improve five-year survival rates (Ji et al., 2007). In general, TwHF is effective in reducing the incidence of rejection after organ transplantation and in maintaining the long-term stability of organ function. It has only mild adverse reactions and is suitable for long-term use. However, the use of TwHF against rejection after organ transplantation remains mostly in the experimental stage, and there needs to be further investigation of its pharmacological mechanism and possible adverse reactions to facilitate its future clinical application.

2.5 Inflammatory bowel diseases

Inflammatory bowel diseases are chronic inflammatory disorders of the gastrointestinal tract, such as Crohn's disease and ulcerative colitis. The conventional treatment includes inhibition of the inflammation with corticosteroids, immunosuppressants, and antagonists of tumor necrosis factor (TNF), a proinflammatory cytokine; however, some of these have been associated with risks for infection and malignancy (Lichtenstein et al., 2012). Recently, there has been increased use of complementary and alternative medicine for inflammatory bowel disease patients, with TwHF one of the most frequently used examples of this (Ng et al., 2013; Phatak et al., 2019). In a study of patients with active Crohn's disease, a rapid decline in the Crohn's Disease Activity Index scores was observed during the first eight weeks of treatment with T2 pills, a major constituent of extracts of TwHF, with a significant rapid decrease in serum levels of C-reactive protein (CRP), TNF-α, and interleukin (IL)-1β after treatment, and endoscopic improvements observed at Week 12 (Ren et al., 2007). TwHF has also been used for inflammatory bowel diseases after surgery. A randomized controlled trial found that TwHF provided similar maintenance of the remission of postoperative Crohn's disease to that with mesalazine, with no significant differences in clinical relapse between the two groups (Tao et al., 2009). Another study found that patients with postoperative Crohn's disease, who were treated with TwHF, had lower recurrence rates than those treated with sulphasalazine (Liao et al., 2009).

3 Anti-inflammatory and immunosuppressive mechanisms

3.1 Regulation of T cells

T cells, which are produced by bone marrow hematopoietic stem cells, play an important role in immune regulation, and their dysfunction is associated with many inflammatory diseases. When stimulated by antigens in peripheral lymphoid organs, T cells can differentiate into subsets of cells with different effector functions. TwHF promotes T cell apoptosis, thereby playing an immunosuppressive role. It has recently been reported that TwHF relieved the symptoms of colitis in a mouse model, reducing the release of proinflammatory factors including IL-1β, IL-6, and TNF-α (Yang et al., 2019). Flow cytometry revealed an increase in the apoptosis of $CD3^+CD4^+$ T cells and $CD3^+CD8^+$ T cells in the peripheral blood and spleen of the mice treated with TwHF. Bax expression in the T cells decreased, which may have been a factor in the promotion of the $CD3^+$ T cell apoptosis (Yang et al., 2019).

In a mouse model of psoriasis, TwHF treatment reduced the number of T helper 17 (Th17) cells in the spleen, with no significant changes in the numbers of other T cell subsets (Th1, Th2, or regulatory T cells

(Treg)), as well as reducing the expression of Th17 proinflammatory factors (Zhao et al., 2016). A study of the effects of TwHF in a mouse model of colitis found that it downregulated the expression of IL-17 by inhibiting the IL-6/signal transducer and activator of transcription 3 (STAT3) pathway, and alleviating the symptoms of colitis (Li et al., 2010). These findings suggest that TwHF may inhibit the differentiation of T cells to Th17, thus reducing the Th17-mediated inflammatory response. Studies have also reported that TwHF helps relieve intestinal inflammation in patients with Crohn's disease (Ng et al., 2013; Phatak et al., 2019). The expression of forkhead box protein 3 ($Foxp3^+$) Tregs and IL-10 increased in the intestinal mucosa after treatment with TwHF, suggesting that TwHF's therapeutic role may be through promoting the differentiation of T cells into Treg cells and reducing the intestinal inflammatory response (Li GW et al., 2014). TwHF has also been shown to regulate the ratio of $CD4^+$ and $CD8^+$ cells, making the immune system in a suppressive situation (Zhang, 2007).

3.2 Regulation of B cells

B lymphocytes are antibody-producing cells in the immune system. After activation by antigen stimulation, they proliferate, producing antibodies that mediate specific humoral immune responses. Treatment with TwHF can inhibit the proliferation of B lymphocytes. For example, TwHF treatment was found to inhibit the proliferation of B cells infected with the Epstein–Barr virus, perhaps related to the decreased expression of latent membrane protein 1 (LMP1) in the B cells (Zhou et al., 2015). In addition, TwHF can reduce antibody levels and alleviate donor-specific antibody-mediated renal injury. In a study of kidney transplant patients, the treatment with triptolide, an active extract of TwHF, was shown to inhibit the differentiation of B cells into $CD138^+CD27^+$ plasma cells and the secretion of IgA, IgG, and IgM from plasma cells, with decreases in the number of B cells in the spleen and the infiltration of various inflammatory cells in the transplanted kidney (Zhao et al., 2018). These findings suggest that triptolide could be used as a novel treatment for antibody-mediated allogeneic rejection.

3.3 Regulation of dendritic cells

Dendritic cells (DCs) are the most effective professional antigen-presenting cells and play an important role in the induction of the immune response and in immune tolerance. DCs originate in the bone marrow and can migrate in the blood to almost any tissue in the body. Chemokine receptor 7 (CCR7) promotes the migration of DCs to lymph nodes and the spleen; there, the DCs present antigens to T cells, which in turn elicit the immune response. Thus, inhibiting the migration of DCs to tissues and secondary lymphoid organs is an effective way to induce immunosuppression and immune tolerance. Liu et al. (2007) reported that the treatment with TwHF reduced the expression of CCR7 and cyclooxygenase 2 (COX-2), as well as inhibiting chemokine CC ligand 19/macrophage inflammatory protein-3β (CCL19/MIP-3β)-induced DC migration, both in vitro and in vivo, thereby reducing the production of proinflammatory factors. Chen et al. (2015) demonstrated that triptolide could inhibit the maturation of DCs by increasing CCR5 and reducing CCR7 expression, which then affected cytokine secretion and chemotaxis.

Studies have shown that triptolide can regulate the differentiation of DCs and change the proportions of the different types of DCs. Triptolide can promote the differentiation of spleen DCs to $CD11c^{low}$ DCs, and then promote the transformation of Th1 cells into Th2 cells, inhibiting the immune function of T cells (Yan et al., 2012). Conversely, Liu et al. (2004) reported that triptolide treatment did not change the phenotype of the DCs, but played an immunosuppressive role by promoting the apoptosis of DCs and reducing their number.

3.4 Regulation of macrophages

Macrophages are the body's first line of defense against foreign invasion and play important roles in tissue development and the maintenance of tissue homeostasis (Stefater et al., 2011). For this, macrophages differentiate into different phenotypes according to the signals they receive from the environment, a phenomenon known as macrophage polarization (Boorsma et al., 2013). Macrophages are mainly classified as the M1 phenotype (classically activated macrophages) or the M2 phenotype (alternatively activated macrophages). It is generally accepted that M1 macrophages secrete the proinflammatory factors IL-12, IL-1β, TNF-α, and IL-6, which enhance the immune response of Th1. They also secrete chemokines, which can promote macrophage

migration. In addition, M1 macrophages participate in the positive immune response by function as an immune monitor. The M2 type of macrophage, which is only weakly antigen-presenting, releases the inflammatory factors IL-10 and transforming growth factor-β (TGF-β) and limits the inflammatory response in the late stage of immune response, thereby promoting tissue repair and wound healing (Murray, 2017).

Jiang et al. (2018) reported that treatment with celastrol, an active extract of TwHF, reduced the expression of inflammatory cytokines and protected against acute ischemic stroke-induced brain injury. Their in vitro and in vivo experiments showed that celastrol promoted M2 phenotype polarization, thereby reducing brain tissue inflammation. This study suggested that M1 macrophages clear damaged cells at the early stage of the immune response and play a role in immune monitoring, but if they are activated for a long time, they release a large number of proinflammatory factors that can aggravate tissue inflammation or cause tissue damage (Jiang et al., 2018). Thus, the polarization of macrophages to the M2 phenotype by TwHF treatment can control the inflammatory response and promote tissue repair. Another inflammatory models have also shown that TwHF regulated macrophage polarization, reducing the number of M1 type macrophages and inhibiting the inflammatory response (Luo et al., 2017).

TwHF treatment can also promote the apoptosis of macrophages. In a mouse model of chronic colitis, treatment with TwHF reduced the expression of the anti-apoptotic proteins B-cell lymphoma-2 (Bcl-2) and Bcl-x via the IL-6/STAT3/suppressor of cytokine signaling-3 (SOCS3) pathway and promoted the apoptosis of intestinal mucosal propria mononuclear cells (Li et al., 2013). Since that study, the mechanism has been confirmed by in vitro experiments of colon cells from patients with Crohn's disease (Li et al., 2013).

3.5 Regulation of pyroptosis

Pyroptosis, also known as inflammatory necrosis, is a newly discovered mode of programmed cell death. The process can be summarized as follows. When inflammasome complexes receive pathogenic inflammatory signals, they activate a variety of caspases, which cleave gasdermin D (GSDMD), a member of gasdermin family. This releases the gasdermin-N domain, which binds to phosphoinositides in the plasma membrane and generates membrane pores, resulting in a change in cell osmotic pressure, thereby fracturing the membrane and eventually causing cell death (Shi et al., 2017; Xu et al., 2018). Pyroptosis is emerging as a general innate immune effector mechanism that helps to maintain homeostasis; however, excessive pyroptosis can release inflammatory factors that extend the inflammatory response, resulting in a disease state (Strowig et al., 2012). Inflammasome complexes play an important regulatory role in pyroptosis. Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) is thought to be the most important inflammasome complex that triggers pyroptosis, and it has been proposed as a potential target for the treatment of inflammatory diseases (von Moltke et al., 2013; Lamkanfi and Dixit, 2014).

In a mouse model of colitis induced by dextran sulfate sodium, TwHF relieved the symptoms of septic shock induced by lipopolysaccharides and inhibited the inflammatory response by inhibiting cell pyroptosis (Yu et al., 2017). The study confirmed that tripterine reduced the production of reactive oxygen species (ROS) and inhibited the formation of the NLRP3 inflammasome and its aggregation with apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), thereby blocking the pyroptosis process and leaving the body in an immunosuppressed state (Yu et al., 2017).

During pyroptosis, active caspase-1 can cause pro-IL-1β to become mature IL-1β. Following cell rupture, the IL-1β can be secreted extracellularly, promoting an inflammatory response. Several studies have shown that TwHF inhibits the production of IL-1β, with a recent study suggesting that this process may be related to inhibition of the activation of the NLRP3 inflammasome complex and the reduction of pyroptosis (Liu et al., 2007; Xin et al., 2017).

3.6 Regulation of molecular expression on the cell surface

T lymphocyte activation requires two signals: an antigen-specific signal that comprises antigen peptide, the major histocompatibility complex (MHC), and T cell antigen receptors; and a signal that includes B7 family proteins, CD28, CD40, intercellular adhesion molecule (ICAM), and other costimulatory molecules.

Renal tubular epithelial cells can express MHC II and costimulatory molecules, such as CD40 and B7 and so are regarded as antigen-presenting cells. C3 is secreted mainly by liver cells and is considered to be an immune adjuvant that plays an important role in activating and triggering the immune response. Studies have shown that selectively regulating the expression of these molecules can effectively regulate the immune state and therefore treat autoimmune diseases. When renal tubular epithelial cells were stimulated by TNF-α, this increased the expression of C3, CD40, and B7h on the cell surface; treatment with TwHF inhibited the expression of these molecules to a greater extent than treatment with cyclosporin A (CsA) or tacrolimus (FK506) (Hong et al., 2002). An in vitro study by Chen et al. (2005) showed that TNF-α stimulation upregulated the expression of B7 family proteins on the surface of human and mouse renal tubular epithelial cells, with B7 homolog 1 (B7-H1) showing the greatest increase. TwHF has also been shown to downregulate the transcription and protein expression of B7-H1 by inhibiting the nuclear factor-κB (NF-κB) pathway, and to regulate the expression of other costimulatory molecules such as MHC II and ICAM, thereby inhibiting the activation of T cells (Li et al., 2002).

3.7 Regulation of the expression of microRNA

MicroRNAs (miRNAs) are small non-coding RNAs composed of 18 to 25 nucleotides that play an important regulatory role in gene expression, especially during the post-transcriptional phase. They are also involved in cell proliferation, differentiation, apoptosis, and development, and in other biological processes (Lee and Vasudevan, 2013). In recent years, evidence has accumulated that miRNA is associated with a variety of inflammatory and autoimmune diseases (Sun et al., 2017). The miRNA miR-155 has a strong ability to regulate immune cells. As a target of miR-155, srchomology 2 (SH2)-containing inositol phosphatase 1 (SHIP-1) is an effective inhibitor of many inflammatory pathways and plays an important role in regulating T cell differentiation and in maintaining balance in T cell subsets. In a model of ileocaecal resection in IL-$10^{-/-}$ mice, triptolide ameliorated the inflammation associated with the postoperative intestinal anastomosis and inhibited the expression of inflammatory factors by inhibiting the miR-155/SHIP-1 pathway (Wu et al., 2013). Another study has shown that treatment with tripterine can reduce lipopolysaccharide-induced inflammatory damage by upregulating miR-146a, which may act through inhibiting the c-Jun N-terminal kinase (JNK)/NF-κB pathway (Xiong et al., 2018).

3.8 Protection of the endothelial barrier function

The endothelial barrier function is critical for maintaining homeostasis in tissues, and its impairment is an important pathological process in many inflammatory diseases. When endothelial cells are damaged, there is an increase in capillary permeability and plasma exudation, which results in swelling of the joint (Middleton et al., 2004). Breakdown of the endothelial barrier function can also promote the adhesion of neutrophils to vascular endothelial cells, resulting in abnormal coagulation function, microvascular leakage, tissue hypoperfusion, and ultimately multiple organ failure (Opal and van der Poll, 2015; Gao et al., 2019). The permeability of endothelial cells increases with lipopolysaccharide and interferon-γ stimulation. Treatment with TwHF has been shown to inhibit the formation of endogenous peroxide nitrite, ameliorating its damage to endothelial cells; this reduces the permeability of the endothelial cells, thereby protecting the function of the endothelial barrier. Repairing integrated endothelial barrier inhibits the further expansion of the inflammatory response (Wu et al., 2009).

4 Methods for reducing the toxicity of TwHF and enhancing its efficacy

Although TwHF has significant clinical efficacy, its toxic and side effects cannot be ignored because its active component is also its toxic ingredient. Reported adverse reactions include liver and kidney toxicities, gastrointestinal reaction, damage to the reproductive system, and blood system toxicity. The recent interest in TwHF has resulted in extensive research into how to reduce its toxicity and enhance its curative effect, with many proposed methods to achieve these.

4.1 Compatibility in traditional Chinese medicine

The compatibility approach of traditional Chinese medicine, which is one aspect of its holistic

viewpoint, can be used to reduce the toxicity of TwHF. Using this approach, each adverse reaction can be alleviated by selecting the appropriate compatible Chinese medicines. For example, hepatotoxicity is the most common adverse reaction to TwHF. The mechanism for liver toxicity induced by TwHF may be related to the oxidative stress mediated by the TwHF itself. When TwHF causes acute liver injury, a large amount of ROS is produced in the body; these damage the DNA and proteins in liver cells, resulting in impaired liver cell function (Li J et al., 2014). Studies have also shown that TwHF promotes liver cell apoptosis by regulating the expression of apoptosis-related proteins, leading to liver injury (Mei et al., 2005; Yao et al., 2008). Glycyrrhiza is the most commonly used compatible Chinese medicine for reducing the liver toxicity of TwHF. Its functions include anti-oxidation, mitochondria protection, and anti-apoptosis, and it protects the membranes of liver cells, reducing liver steatosis and necrosis, and thus improving liver function. Glycyrrhiza also affects the level and activity of the enzyme cytochrome P450 (CYP450), which plays an important role in drug metabolism. Glucuronic acid, a hydrolysate of glycyrrhiza, binds with toxins, such as diterpenoid compounds and alkaloids, and then eliminates them from the body. These characteristics accelerate the metabolism of TwHF in vivo and reduce its toxicity (Cao et al., 2015).

However, there is no unified standard for the optimal ratio of glycyrrhiza and TwHF for reducing toxicity and increasing the effectiveness of the TwHF. Du et al. (2008) administered TwHF and glycyrrhiza decoctions to rats at different dosage ratios for four weeks via gavage. The blood biochemical results and calculations confirmed that the dosage ratio of TwHF to glycyrrhiza with the lowest toxicity was 60:9 (Du et al., 2008). Ma et al. (2017) investigated the attenuating effect on L02 liver cells of an alcohol infusion of TwHF and glycyrrhiza by measuring liver cell activity with high-intensification analysis technology. They found a ratio of TwHF to glycyrrhiza of 3:1 or 6:1 reduced hepatocellular toxicity. However, given the first-pass effect of glycyrrhiza in the body, it is reasonable to choose a ratio with a higher proportion of glycyrrhiza (such as 3:1) to ensure the reduction of toxicity. In rat models, the dosage ratio of TwHF to glycyrrhiza with the lowest toxicity was found to be 6:1 (Ma et al., 2014) and 60.0:19.6 (Zhou and Liang, 2009; Song et al., 2014). In a clinical study of patients with rheumatoid arthritis, the best ratio of TwHF to glycyrrhiza was 1:2 (Li et al., 2006). These studies have confirmed the toxicity reduction effect of this compatibility, but further study is needed to establish the optimal proportion of TwHF to glycyrrhiza.

Chinese herbs for regulating Qi and harmonizing the stomach are often used together for adverse reactions of the digestive tract. These include *Pinellia ternata*, *Bletilla striata*, and modified Liuwei Dihuang soup. Commonly used herbs for reproductive toxicity include *Epimedium*, *Polygonum multiflorum*, *Fructus Ligustri Lucidum*, and wolfberry.

4.2 Processing methods of medicinal herbs

Processing refers to the effective traditional method for reducing the toxicity of Chinese herbs according to the theory of traditional Chinese medicine and the nature of the medicinal materials. It uses methods such as watering, firemaking, and adding auxiliary materials. The traditional method of detoxifying TwHF is through boiling in water. As the boiling time increases, the toxicity of TwHF decreases gradually; however, its anti-inflammatory activity also decreases. Comprehensive consideration suggests that the toxicity and pharmacological activity reach the optimal state after 1 h of boiling. Because the root bark has the highest toxicity, it must be removed during processing, leaving the xylem, which is less toxic.

Alkaloids are the main toxic components in TwHF. Studies have tried various processing methods to treat TwHF, with changes in the alkaloids tested to measure the reduction in toxicity. The content of alkaloids ranged from high to low in the products processed by vinegar-processing, wine-processing, light-frying, and braising. This suggested that braising was the best method for reducing toxicity (Chen, 2015). It has also been reported that sheep blood processing (boiling TwHF with sheep blood) had a good effect on reducing toxicity. Recent studies of traditional Chinese medicine have investigated decoctions of pieces of TwHF processed with various other substances, including mung beans, white peony root, and honeysuckle.

4.3 Improvement of dosage form

The toxicity and efficacy vary between the different forms of TwHF administered as drugs. The

common dosage forms of TwHF include decoction, syrup, granule, tablet, liquid extract, liniment, tincture, and ointment. In recent years, microemulsions, microcapsules, dropping pills, sustained-release agents, and other dosage forms have been developed to increase the dispersal, solubility, and bioavailability of TwHF and to reduce its toxicity and side effects (He et al., 2017). The traditional dosage form of TwHF is decoction. The tablet is convenient to take, and the processing reduces the toxicity; however, adverse reactions of the tablet have been reported for the digestive system, cardiovascular system, and blood system. In addition to the traditional oral administration, topical preparations of TwHF have become a focus of research. Compared with oral administration, topical administration reduced gastrointestinal reactions and liver and kidney toxicities, and avoided the first-pass effect of liver; in addition, the blood concentration remained constant and this form required less frequent administration. Various physical permeability promotion technologies have been developed to improve the transdermal permeability of drugs, such as microacupuncture and ion introduction, and permeability promotion formulations such as barb agents, gel agents, and nano carriers have also been developed (Gu et al., 2018). Although new dosage forms have made rapid progress in recent years, most remain at the research stage and have not had wide clinical use.

5 Prospects for the future

TwHF has attracted increasing research, both domestic and foreign, because of its anti-inflammatory and immunosuppressive pharmacological characteristics and clinical effects in autoimmune-related and inflammatory diseases. Many recent studies have investigated its pharmacological mechanisms. These have suggested various anti-inflammatory and immunosuppression mechanisms for TwHF, but the exact or main mechanism remains unclear. There have also been many reports on the adverse reactions of TwHF, and its toxic and side effects cannot be ignored. In our opinion, future studies of TwHF should focus on two aspects. First, many immune-mediated inflammatory diseases still have no effective clinical treatment. Given that TwHF is a good immunosuppressive agent, its potential anti-inflammatory and immunosuppressive mechanisms should be explored to extend its clinical application. Paraquat poisoning-induced acute lung injury is thought to be associated with a strong and persistent inflammatory response (Wang et al., 2017; Feng et al., 2018; Xu and Lu, 2019). Our group has reported that an acquired immune deficiency syndrome (AIDS) patient who ingested a lethal dose of paraquat had a good prognosis (Shang and Lu, 2015). Patients with AIDS are known to have immunodeficiency, whose immune system is suppressed, and that case could indirectly support the effectiveness of immunosuppressive therapy in treating patients with paraquat poisoning (Lu, 2018). Our group will further explore the effect of TwHF on paraquat poisoning. Second, efforts should be focused on reducing the toxicity and side effects of TwHF. Toxicity can be reduced and efficiency increased through the application of drug compatibility, improvements to the purification process, and using TwHF in combination with modern biotechnology. This should ensure the safety of its clinical use. In these ways, the potential clinical application of TwHF can be maximized, allowing it to be used for solving more difficult clinical problems.

Contributors

Cong-ying SONG and Yuan-qiang LU participated in the design. Cong-ying SONG and Ying-ge XU wrote this article. Yuan-qiang LU checked the final version. All authors have read and approved the final manuscript.

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Compliance with ethics guidelines

Cong-ying SONG, Ying-ge XU, and Yuan-qiang LU declare that they have no conflict of interest.

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中文概要

题　目：雷公藤在免疫介导的炎症疾病中的应用：研究进展及展望

概　要：雷公藤作为中国传统药材的瑰宝，具有较强的抗炎及免疫抑制作用，临床上广泛应用于类风湿性关节炎、系统性红斑狼疮、肾脏疾病等自身免疫性及炎症性疾病。由于雷公藤对于自身免疫疾病疗效显著，且没有激素的副作用，近年来备受国内外研究者关注，大量研究开始探究其抗炎及免疫抑制的潜在机制。而雷公藤本身也存在毒副作用，限制了其在临床更广泛的应用。本文总结了近年来雷公藤在免疫相关炎性疾病临床应用情况，雷公藤抗炎和免疫调节的机制以及目前雷公藤减毒的方法，旨在更好地帮助临床医生及科研工作者理解雷公藤的生物特性及作用机制，为临床应用及推广提供参考依据。

关键词：雷公藤；抗炎；免疫抑制