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Applications Of Tripterygium Wilfordii Hook. F. And Its Preparations In Inflammatory Disorders And Their Mechanisms Of Action

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Abstract
Chinese herbal medicine called Tripterygium wilfordii Hook. F. (TwHF) has a lot of metabolites. It has drawn increasing attention in studies and clinical research because of its established anti-inflammatory and immune-regulating properties. Traditional Chinese medicine may be seen in the extraction and processing of TwHF for medicinal use. TwHF, however, is poisonous. The development of TwHF medicines now depends on optimization of TwHF formulations. In order to serve as a guide for Tripterygium wilfordii Hook F's potential future therapeutic use, this review provides an overview of the plant's current clinical use as well as the findings of investigations into its mechanisms and toxicity.

Key words: *Autoimmune illnesses, Tripterygium wilfordii Hook. F., alkaloids, immunoregulatory mechanisms, toxicity.*

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I. Introduction

Tripterygium wilfordii Hook. F. (TwHF), a plant belonging to the vine-like plant family Celastraceae, was first mentioned in the Compendium of Materia Medica of the 16th century and is a significant medication in traditional Chinese medicine [1]. TwHF was previously supplied as a decoction; however, in light of substantial study on this medication, its extracts are being utilized more frequently in clinical settings. There have been more than 70 chemical components discovered thus far, including alkaloids, diterpenoids, triterpenoids, etc., but the most effective and extensively researched derivatives are triptolide and tripterine. TwHF has garnered the interest of several researchers in recent years, with many studies examining the probable reasons for its anti-inflammatory and immunosuppressive benefits. TwHF has a considerable curative impact on autoimmune illnesses with no hormone-related adverse effects. TwHF's proven toxicity and adverse effects, however, prevent it from being used in more clinical settings [1].

This review discusses TwHF's anti-inflammatory and immunoregulatory mechanisms, therapeutic applications for immune-related inflammatory illnesses during the last several years, and strategies being used to lessen its toxicity. The review's objectives are to improve understanding of the biological properties and processes of this medication and to serve as a resource for its therapeutic use and promotion.

II. Application in medicine for immune-related inflammatory illnesses

Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune illness, and the currently available disease-modifying antirheumatic medications and biological agents used to treat it are costly and of poor effectiveness. TwHF, sometimes referred to as "the Chinese herbal hormone," has been shown to be successful in treating the ailment. TwHF was as successful as MTX and outperformed MTX monotherapy for managing disease action, according to an investigation that treated rheumatoid arthritis individuals with either TwHF, methotrexate (MTX), or an amalgam of the two and monitored them over a 24-week time frame. The merged intervention also substantially raised the beneficial impact, resulting in a success rate of 76.8% [2].

The combo of TwHF and MTX substantially reduced the manifestations of arthritis and regulated the exertion of individuals with rheumatoid arthritis, with no enhancement in detrimental responses contrasted to the single medication therapy approaches, according to a meta-analysis of six randomized controlled trials (643 individuals) [3]. TwHF and MTX together may therefore be a secure and successful therapy for rheumatoid arthritis. Though exploring TwHF in conjunction with other medications is still necessary.

Renal disease

For a variety of kidney conditions, such as chronic glomerulonephritis, nephrotic syndrome, diabetic nephropathy, and lupus nephritis, TwHF offers high effectiveness. Tripterygium glycosides, which are generated from TwHF, can lessen the amount of protein in the urine and enhance the pace at which endogenous creatinine is cleared, providing a demonstrable rehabilitative and preventive impact on kidney performance in comparison to the standard intervention for diabetic nephropathy. Recent clinical investigations have demonstrated that tripterygium glycosides and irbesartan together have a more effective therapeutic effect for immunoglobulin A (IgA) nephropathy than either agent alone. These two medications worked better together as protection against renal podocyte damage than they did alone, slowing the progression of the illness [4].

Hormones and immunosuppressive medications are now used to treat recalcitrant nephrotic syndrome, but prolonged administration of these medications can have significant toxic and side effects, and the disorder has a poor prognosis and an elevated likelihood of relapse. TwHF exhibits positive therapeutic benefits in refractory nephrotic syndrome and behaves similarly to a hormone but without hormonal adverse effects. Patients with refractory nephrotic syndrome were studied, and tripterygium glycosides and mycophenolate mofetil were juxtaposed with mycophenolate mofetil monotherapy [1]. The simultaneous administration of mycophenolate mofetil and tripterygium glycosides may be a successful therapeutic technique for refractory nephrotic syndrome, according to an assessment of kidney activity, which revealed a greater curative outcome with the combined medication and a much reduced relapse incidence.

Rejection following transplantation of organs

Considering that TwHF has a potent immunosuppressive impact, it has been utilized to prevent the refusal response following organ donation. TwHF is generally efficient at lowering the likelihood of organ rejection following transplantation and preserving the long-term viability of organ activity. It is safe for lengthy usage and has just moderate side effects. Nevertheless, TwHF's usage for preventing rejection following organ donation is still mainly experimental, so additional research into its pharmacological mechanism and potential side effects is required before it can be used in clinical settings.

Inflammatory bowel diseases

Chronic inflammatory conditions like Crohn's disease and ulcerative colitis are examples of inflammatory bowel diseases. Corticosteroids, immunosuppressants, and antagonists of the proinflammatory cytokine tumor necrosis factor (TNF) are all used in traditional medication to reduce inflammation. Nevertheless, some of these have been linked to an increased threat of infection and cancer [5]. TwHF is one of the most widely utilized forms of this, with the usage of supplementary and unconventional therapy for inflammatory bowel disease individuals increasing significantly [6, 7]. In an investigation of individuals with persistent Crohn's disease, the serum levels of C-reactive protein (CRP), TNF-, and interleukin (IL)-1 significantly dropped after medication, and endoscopic enhancements were seen at week twelve. This was followed by an immediate reduction in the Crohn's Disease Activity Index scores throughout the first eight weeks of medication with T2 pills, a key component of extracts of TwHF [8]. Inflammatory bowel illnesses have also been treated with TwHF following surgery.

III. Immunosuppressive and anti-inflammatory pathways

Control of T cells

T cells, which are created by hematopoietic stem cells in the bone marrow, are crucial for immunological control, and their malfunction is linked to with a lot of inflammatory illnesses. T cells can develop into subsets of cells with various effector roles when activated by antigens in peripheral lymphoid organs. TwHF suppresses the immune system by promoting T cell death.

According to a recent study, TwHF reduced the production of proinflammatory factors including IL-1, IL-6, and TNF-α while alleviating the symptoms of colitis in an animal model [9]. The peripheral blood and spleen of the mice given TwHF showed a spike in the apoptosis of CD3+ CD4+T cells and CD3+CD8+ T cells, according to flow cytometry. The T cells' lower Bax expression may have contributed to the enhancement of CD3+ T cell death [9]. TwHF therapy decreased the production of Th17 proinflammatory markers and the number of T helper 17 (Th17) cells in the spleen in a mouse model of psoriasis. There were no appreciable changes in the numbers of other T cell subsets (Th1, Th2, or regulatory T cells (Treg)), however [10]. TwHF was discovered to have positive impacts on the manifestations of colitis in a mouse model of the disease by blocking the IL-6/signal transducer and activator of transcription 3 (STAT3) pathways and reducing the production of IL-17 [11].

These results imply that TwHF may prevent T cells from differentiating into Th17, hence lowering the Th17-mediated inflammatory reaction. Additionally, studies show that TwHF reduces intestinal inflammation in those with Crohn's disease [6, 7]. After TwHF administration, the expression of forkhead box protein 3

(Foxp3+) Tregs and IL-10 elevated in the intestinal mucosa, indicating that TwHF may have therapeutic effects by encouraging T cells to differentiate into Treg cells and lowering the inflammatory reaction in the gut [12]. TwHF has been demonstrated to control the ratio of CD4+ to CD8+ cells, suppressing the immune system [13].

Control of B cells

The immune system's B lymphocytes are the cells that make antibodies. Following antigen-stimulated activation, they multiply and produce antibodies that regulate certain humoral immune responses. TwHF therapy can prevent B lymphocyte proliferative growth. For instance, it was shown that TwHF therapy inhibited the growth of B cells infected with the Epstein-Barr virus, which may be connected to the B cells' reduced production of latent membrane protein 1 (LMP1) [14]. TwHF can also lower antibody levels and treat kidney damage brought on by donor-specific antibodies. Triptolide, a chemically active extract of TwHF, has been demonstrated to inhibit the division of B cells into CD138+CD27+ plasma cells and the release of IgA, IgG, and IgM from plasma cells in an experiment of kidney transplant recipients. This resulted in a decline in the amount of B cells in the spleen and the infiltration of numerous inflammatory cells in the transplanted kidney [15]. These results imply that triptolide may represent a unique therapeutic approach for antibody-mediated allogeneic rejection.

Control over dendritic cells

The best professional antigen-presenting cells are dendritic cells (DCs), which are crucial for both the elicitation of an immunological reaction and immune tolerance. In the circulation, DCs may go from the bone marrow to practically every tissue in the body. Chemokine receptor 7 (CCR7) encourages DCs to go to the spleen and lymph nodes, where they provide antigens to T cells, which then trigger an immunological reaction. Therefore, preventing DCs from migrating to tissues and secondary lymphoid organs is a useful method to promote immunological tolerance and immunosuppression. According to an investigation, TwHF treatment decreased the expression of CCR7 and cyclooxygenase 2 (COX-2) and inhibited DC migration that was provoked by the chemokine CCL19/macrophage inflammatory protein-3β (CCL19/MIP-3β), both in vitro and in vivo. This decreased the creation of proinflammatory elements [16].

Triptolide has been proven in studies to control DC differentiation and alter the ratios of the various DC subtypes. Triptolide can enhance spleen DC development into CD11clow DCs, and ultimately enhance Th1 cell differentiation into Th2 cells, decreasing T cell immunity [17]. On the other hand, according to another study, triptolide administration had no effect on the phenotypic of the DCs but instead suppressed the immune system by increasing the death of DCs and lowering their population [18].

Control over macrophages

Macrophages perform crucial functions in tissue growth and the preservation of tissue homeostasis and serve as the body's first line of defense against foreign invasion. For this reason, a process known as macrophage polarization occurs in which macrophages divide into various phenotypes in accordance with the signals they receive from the environment [19]. The two primary phenotypes of macrophages are M1 phenotypes (classically activated macrophages) and M2 phenotypes (alternatively activated macrophages). The proinflammatory substances: IL-12, IL-1, TNF-α, and IL-6 that M1 macrophages release are known to boost Th1 immune reaction. Additionally, they release chemokines that might encourage macrophage movement. Additionally, by acting as an immunological monitor, M1 macrophages contribute to the beneficial immune response. The M2 type of macrophage, which only weakly presents antigens, produces IL-10 and transforming growth factor-β (TGF-β), which restrict the inflammatory response in the late stage of the immune response and aid in tissue regeneration and wound healing [20].

According to a research, using celastrol, an active extract of TwHF, decreased the production of pro-inflammatory cytokines and provided protection against brain damage brought on by acute ischemic stroke [21]. This in vitro and in vivo research demonstrated that celastrol enhanced M2 phenotypic polarization, which in turn decreased inflammation in the brain tissue. According to this study, M1 macrophages remove injured cells during the beginning of the immune response and assist in immunological monitoring, but if they are active for an extended period of time, they produce a lot of proinflammatory chemicals that might exacerbate tissue inflammation or result in tissue damage [21]. As a result, polarizing macrophages to the M2 phenotype with TwHF therapy can reduce inflammation and aid in tissue healing. TwHF was also demonstrated to modulate macrophage polarization in additional inflammatory models, lowering the proportion of M1 type macrophages and suppressing the inflammatory response [22].

Additionally, TwHF therapy might encourage macrophage death. Administration with TwHF decreased the expression of the anti-apoptotic proteins B-cell lymphoma-2 (Bcl-2) and Bcl-x through the IL-6/STAT3/suppressor of cytokine signaling-3 (SOCS3) pathway in a rat model of chronic colitis and increased

the death of intestinal mucosal propria mononuclear cells [23]. Since that investigation, in vitro tests using colon cells from Crohn's disease patients have verified the process [23].

Control over pyroptosis

The process of planned cell death known as pyroptosis, commonly referred to as inflammatory necrosis, is relatively recent. Following is a summary of the procedure. A number of caspases are activated by pathogenic inflammatory signals received by inflammasome complexes, which then cleave a member of the gasdermin family called gasdermin D (GSDMD). When the gasdermin-N domain is released, it attaches to phosphoinositides in the plasma membrane and creates membrane holes, which changes the osmotic pressure inside the cell and eventually breaks down the membrane, leading to cell death [24, 25].

TwHF reduced the signs of septic shock brought on by lipopolysaccharides in a mouse model of colitis brought on by dextran sulfate sodium, and it additionally stopped the inflammatory response by preventing cell pyroptosis [26]. Tripterine was found to hinder the development of the NLRP3 inflammasome and its consolidation with the apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), which prevented pyroptosis and left the body in an immunosuppressed state, according to the research [26]. Active caspase-1 can induce pro-IL-1β to develop into mature IL-1β during pyroptosis. IL-1β can be released extracellularly after cell dissection, triggering an inflammatory reaction. Numerous studies have demonstrated that TwHF reduces IL-1β production, and a more recent research raises the possibility that this effect may be mediated by blocking the activation of the NLRP3 inflammasome complex and reducing pyroptosis.

Control of cellular surface molecular expression

Two signals are necessary for T lymphocyte activation: an antigen-specific signal composed of the antigen peptide, the major histocompatibility complex (MHC), and T cell antigen receptors; and a costimulatory signal composed of the B7 family of proteins, CD28, CD40, intercellular adhesion molecule (ICAM), and other molecules. Renal tubular epithelial cells are thought of being antigen-presenting cells since they may express MHC II and costimulatory molecules like CD40 and B7. C3 is mostly released by liver cells and is thought to function as an immunological adjuvant, stimulating and initiating the immune reaction. According to studies, it is possible to efficiently control these molecules' expression to cure autoimmune illnesses by modulating the immune system. TNF-α enhanced the expression of C3, CD40, and B7h on the cell surface after stimulating renal tubular epithelial cells, and treatment with TwHF suppressed this expression more than tacrolimus (FK506) or cyclosporin A (CsA) did [27]. TNF-α stimulation increased the expression of B7 family proteins on the outermost layer of human and mouse renal tubular epithelial cells, with B7 homolog 1 (B7-H1) exhibiting the largest increase, according to an in vitro investigation [28]. TwHF has also been demonstrated to influence the production of additional costimulatory compounds such MHC II and ICAM, consequently reducing the activation of T lymphocytes, as well as the transcription and protein expression of B7-H1 by blocking the nuclear factor-κB (NF-κB) pathway [29].

Control over microRNA expression

Small non-coding RNAs known as microRNAs (miRNAs) have 18 to 25 nucleotides and are essential regulators of gene expression, particularly in the post-transcriptional stage. Proof has gathered over the past few years to suggest that miRNA is connected to a number of inflammatory and autoimmune illnesses [30]. Immune cells can be strongly controlled by the miRNA miR-155. As a miR-155 target, srchomology 2 (SH2)-containing inositol phosphatase 1 (SHIP-1) inhibits a variety of inflammatory pathways effectively and is crucial for controlling T cell development and preserving homeostasis in T cell subtypes. Triptolide reduced inflammation related to the postoperative intestinal anastomosis and reduced the production of inflammatory markers by blocking the miR-155/SHIP-1 pathway in an ileocaecal resection model in IL-10 −/− mice [31].

Safeguarding the endothelial barrier's functionality

The protective role of the endothelium layer is essential for preserving tissue stability, and its degradation is a significant pathogenic event for numerous inflammatory disorders. Joint edema happens as a consequence of increased capillary permeability and plasma exudation brought on by injured endothelial cells [32]. In addition to promoting neutrophil adherence to vascular endothelial cells, endothelial barrier dysfunction can also cause aberrant coagulation function, microvascular leakage, tissue hypoperfusion, and eventually major organ dysfunction [33, 34]. Endothelial cells' permittivity is boosted by lipopolysaccharide and interferon-γ activation. Endothelial cell injury caused by endogenous peroxide nitrite has been demonstrated to be mitigated by administration with TwHF. This decreases the accessibility to penetrate of the endothelial cells, preserving the integrity of the endothelial barrier. Integral endothelial barrier restoration prevents the inflammatory reaction from intensifying [35].

Ways to lower TWHF toxicity and increase its efficiency

TwHF has a substantial clinical effectiveness, but because its poisonous element also serves as its active ingredient, its toxicity and side effects cannot be overlooked. There have been reports of liver and renal toxicity, gastrointestinal issues, reproductive system harm, and blood system toxicity. Due to the new interest in TwHF, there has been a great deal of study on ways to lessen its toxicity and increase its therapeutic efficacy, with several strategies being proposed to do so.

Techniques for processing medicinal plants

In accordance with the principles of traditional Chinese medicine and the makeup of the medicinal substances, preparation refers to an efficient conventional procedure for lowering the toxicity of Chinese herbs. It makes use of techniques including watering, starting a fire, and adding supplementary ingredients. Boiling in water is the typical technique of detoxifying TwHF. The toxicity of TwHF steadily diminishes as boiling duration rises, but so does its anti-inflammatory effect. A thorough analysis reveals that after 1 hour of boiling, the toxicity and pharmacological activity are at their peak. Since the xylem is less poisonous, the root bark must be removed during processing since it has the highest level of toxicity.

The principal hazardous elements in TwHF are alkaloids. Different processing techniques have been explored during investigations to treat TwHF, and alterations in the alkaloids have been examined to determine the diminution of toxicity. Additionally, it has been shown that processing sheep blood—which involves heating TwHF with sheep blood—had a positive impact on toxicity reduction. Investigations on tinctures of TwHF pieces treated with different additional ingredients, which includes as mung beans, white peony root, and honeysuckle, have recently been conducted.

Enhancing the dose form

The various TwHF medication formulations have distinct levels of toxicity and effectiveness. Decoction, syrup, granule, pill, liquid extract, liniment, tincture, and ointment are some of the typical TwHF forms of administration. TwHF decoction is the conventional dose form. Although the pill is easy to swallow and the processing lessens its toxicity, detrimental effects on the blood, cardiovascular, and digestive systems have been noted. Investigation has begun to concentrate on topical formulations of TwHF in addition to the conventional oral dosage. Topical treatment decreased gastrointestinal symptoms, liver and kidney toxicity, and the first-pass impact of the liver when in contrast to oral administration. Additionally, the blood levels stayed steady, and this form needed fewer doses of administration. Even while new forms of administration have advanced quickly in the past few years, the most are still in the development phase and have not been widely used in clinical settings.

Future possibilities

Due to its clinical benefits in autoimmune-related and inflammatory disorders as well as its anti-inflammatory and immunosuppressive pharmacological properties, TwHF has drawn increased attention from both local and international researchers. Numerous recent researches have looked into the pharmacological processes involved. These have proposed different immunosuppressive and anti-inflammatory pathways for TwHF, but the precise or primary mechanism is yet unknown. Additionally, there have been several complaints about TwHF's unfavorable consequences and it is impossible to downplay its hazardous and negative consequences. Future research on TwHF should, in our opinion, concentrate on two areas. First, there are still several immune-mediated inflammatory disorders for which there is no curative medical intervention. TwHF is a powerful immunosuppressive drug, hence it is important to investigate its possible anti-inflammatory and immunosuppressive mechanisms. A significant and long-lasting inflammatory response is considered to be linked to paraquat poisoning-induced acute lung damage. Since it is well known that people with AIDS have immunodeficiency and that their immune systems are reduced, this situation may indirectly support the use of immunosuppressive medication to treat people who have been poisoned by paraquat [36]. Second, initiatives should concentrate on lowering TwHF's toxicity and adverse effects. Through the use of drug reliability, enhancements to the cleansing procedure and the use of TwHF in combination with contemporary biotechnology, toxicity may be decreased and productivity can be raised. Its clinical usage should be safe as a result of this. TwHF's potential for therapeutic usage can be increased in this way, enabling more challenging clinical issues to be resolved.

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