

Traditional Chinese Medicines as Immunosuppressive Agents

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Abstract

Introduction: Traditional Chinese Medicines (TCM) have been used for centuries in China to treat various immune-mediated disorders. **Methods:** This review focuses on the clinical and experimental studies that have been performed with TCM as immunosuppressive agents for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), atopic eczema and solid organ transplantation. **Results:** The “thunder god” vine, *Tripterygium wilfordii* Hook F (TWHf), has been extensively used in China to treat SLE and RA. TWHf not only inhibited mitogen-stimulated lymphoproliferation, but its active derivatives have also been shown to inhibit production of proinflammatory cytokines by monocytes and lymphocytes, as well as prostaglandin E2 production via the cyclooxygenase, COX-2, pathway, a potential mechanism of action in patients with RA. Demethylzelastral (TZ-93), a triterpenoid isolated from the root cortex of TWHf, the plant alkaloid berbamine, and the hydrophobic extract of a Chinese herbal decoction, CMX-13, were all shown to be active in prolonging allograft survival in experimental animal models of heart, skin and single lung transplants, respectively. There are few well-designed randomised placebo-controlled clinical trials demonstrating the efficacy of TCM in various diseases. Zemaplyte, a decoction of 10 herbs, has been shown to be efficacious in the treatment of atopic dermatitis in both children and adults in two randomised double-blind placebo-controlled trials. **Conclusion:** There is both laboratory and clinical evidence that the derivatives of many of these herbs may have significant beneficial immunosuppressive effects, however, concerns of toxicity must also be addressed, as exact dosing of the active derivatives is difficult to achieve with the current prescriptions of TCM.

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Introduction

Traditional Chinese Medicines (TCM) are derivatives of natural products that have been used for centuries in China to treat a variety of human disorders, including immune-mediated disorders.¹ The development of immunosuppressive agents with high efficacy and minimal toxicities has been the focus of novel drug research. Current immunosuppressive drugs include corticosteroids, with their effect on growth in children, cataract formation, increased risk to unusual infections, hypertension and osteoporosis; alkylating agents such as cyclophosphamide, chlorambucil or azathioprine, with dose and time-dependent adverse effects on bone marrow, liver and the gonads, as well as a risk of malignancy;² and more recently, cyclosporine and tacrolimus with the potential for nephrotoxicity and neurotoxicity.³⁻⁶ Although TCM have been shown to be effective in various clinical studies,

however, their mechanisms of action have been less well understood. This review focuses on the clinical and experimental studies that have been performed with TCM as immunosuppressive agents for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), atopic eczema and solid organ transplantation.

Systemic Lupus Erythematosus

SLE is an autoimmune disease which affects multiple organ systems. There have been both anecdotal reports⁷ as well as several clinical studies on the use of TCM with and without conventional immunosuppressives for treatment of this disease.^{8,9} A decoction of 21 Chinese herbs (CM) traditionally used in this disease, which included the genera *Prubella*, *Lycium*, *Bletilla*, *Ligustrum*, *Dianthus*, *Myrrrha*, *Eucommia*, *Rehmannia*, *Rosa*, *Rubia*, *Imperata*, *Curculigo*, *Panax*, *Astragalus*, *Codonopsis*, *Dioscorea*, *Nelumbo*,

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Boswellia, *Polygonum*, *Citrus*, and *Glycyrrhiza*, have been reported to induce clinical remission in an SLE patient with long-standing nephrotic syndrome and deteriorating renal function, not controlled by steroids alone.⁷ In one clinical trial looking at the effect of a combination of TCM with steroids and cyclophosphamide, the authors showed that this combination resulted in increased therapeutic efficacy in 41 active SLE patients, as compared to the control group of 35 patients treated only with steroids and cyclophosphamide.⁸ In another study, an “anti-lupus pill” comprising of a decoction of 17 herbs was shown to improve the activity status of SLE patients, defined by an improvement in the skin manifestations, oral ulcers and arthritis, and a decrease in the anti-nuclear antibody titres.⁹ Use of this “anti-lupus pill” in combination with steroids was effective in 92% of the 230 patients studied, and in another 76 patients treated with the “anti-lupus pill” alone, its efficacy was 85%.

The “thunder god” vine, *Tripterygium wilfordii* Hook F (TWHf), has been extensively used in China to treat the autoimmune diseases SLE^{10,11} and rheumatoid arthritis.¹² Ingestion of TWHf in conjunction with steroids has been associated with induction of remission in a patient with severe lupus nephritis.¹³ Moreover, its benefit has also been demonstrated in unblinded studies.^{10,11} Another study using a *Gentiana macrophylla* complex tablet together with prednisolone in 62 patients with SLE was able to demonstrate a 86% remission rate as compared to 32% in the control group of 19 patients treated with prednisolone alone.¹⁴ This herbal complex appeared to improve erythema, arthritis, nephropathy and serological abnormalities such as serum complements.

Unfortunately, there are currently no reported well-controlled randomised clinical trials with TCM in the treatment of SLE. However, several experimental studies looking at the effect of TCM on lymphocyte activation and function in SLE patients, as well as animal models of lupus nephritis have been described. Peripheral blood mononuclear cells (PBMCs) isolated from SLE patients have been shown to increase *in vitro* spontaneous production of IgG. Our group investigated the effect of EX, the ethyl acetate extract of CM, on PBMC production of IgG in 10 children with SLE.⁷ Spontaneous PBMC IgG production was significantly higher in the 10 SLE patients (210 ± 110 ng/mL) compared to 8 controls (64 ± 20 ng/mL). Addition of EX to PBMCs from SLE patients resulted in significant suppression of spontaneous IgG secretion to 96 ± 52 ng/mL (Fig. 1).

In another experiment, Chen and colleagues¹⁵ showed that 6 Chinese herbs, *Atractylodes ovata*, *Angelica sinensis*, *Cordyceps sinensis*, *Liquidum lucidum*, *Codonopsis pilosula* and *Homo sapiens* improved the defective *in vitro*

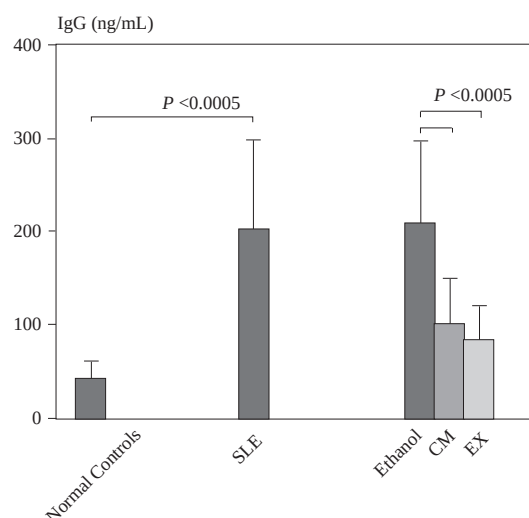


Fig. 1. Suppression of spontaneous IgG production (ng/mL) from peripheral blood mononuclear cells of systemic lupus erythematosus (SLE) patients by the Chinese herbal decoction (CM), and its ethyl acetate extract (EX).

interleukin-2 (IL-2) production in patients with SLE. Further *in vivo* studies in NZB/NZW F1 mice showed that use of *Codonopsis pilosula*, *Cordyceps sinensis* and *Homo sapiens* was able to prolong the life span of these mice which developed spontaneous SLE, as well as to inhibit anti-double stranded DNA antibody production. Refined extracts from the root xylem of TWHf have been shown to be effective in the treatment of lupus nephritis and arthritis in MRL-lpr mice.^{16,17} TWHf was able to decrease the amount of proteinuria in this spontaneous lupus nephritis mouse model, as well as to improve survival. However, no effect was demonstrated in the histopathology of lupus nephritis. Another herb, *stragalin*, was shown to inhibit deposition of ICAM-1, immunoglobulins and C3 in the glomerular capillary walls of MRL-lpr mice.¹⁸

Rheumatoid Arthritis

RA is an autoimmune disease characterised by synovial inflammation where cartilage destruction is perpetuated by the fibrovascular proliferative events in the joint.¹⁹ Various cytokines such as IL-1, IL-6, IL-8 and tumour necrosis factor- α (TNF- α), have been demonstrated in the synovial fluid, and may play a pivotal role in the arthritic process, both in regulating the immune response and in several effector pathways.²⁰⁻²⁵ In experimental models of collagen-induced arthritis, antibodies to IL-1 and TNF- α were able to prevent the onset of the disease,^{26,27} while IL-4 and IL-10 which suppresses IL-1, IL-6 and TNF- α production ameliorated progression.^{28,29} Interferon-gamma (IFN- γ) and transforming growth factor-beta (TGF- β) also protected against progressive arthritis.³⁰

TWHf is the most commonly prescribed TCM in China for the treatment of RA. One placebo-controlled double-

blind trial has clearly demonstrated efficacy.³¹ More than 70 constituents concentrated in the roots of TWHf have been identified, and these include diterpenes, triterpenes, alkaloids, glycosides, b-sitosterol, daucosterol, dulcitol, and wilforonide.³² Its immunosuppressive activity has been attributed to components such as triptolide, triptidiolide, triptonide and triptophenolide.³³

Initial studies looking at the mechanism of action of TWHf in patients with RA showed that it inhibited pokeweed mitogen (PWM)-stimulated IgM and IgG production from peripheral blood mononuclear cells isolated from RA patients.³⁴ Further studies have evaluated the effects of TWHf on cytokine production. TWHf was able to decrease IL-1 production by monocytes stimulated with zymosan, as well as inhibit IL-1 activity on murine thymocyte proliferation.³⁵ The production of other monokines such as TNF- α , IL-6 and IL-8, and the lymphokines, IL-4 and IL-10 were also suppressed by TWHf.³⁶ TWHf was more potent than prednisolone and cyclophosphamide in inhibiting T-cell IL-2 production.³⁷ Its mechanism of action was different from cyclosporine in that it suppressed IL-2 production by CD28-stimulated T-cells, as well as inhibited phorbol 12-myristate 13-acetate (PMA)-induced IL-2R α expression and ionomycin-induced CD40 ligand expression on the T-cells. This study also showed that inhibition of T-cell proliferation by TWHf was not only by downregulation of T-cell receptor signalling pathways, but also by induction of apoptosis.³⁸ The therapeutic efficacy of TWHf could also be explained by its effect on monocyte PGE2 production.^{36,38} Both TWHf and its purified diterpenoid component, triptolide, were able to inhibit PGE2 synthesis in lipopolysaccharide (LPS)-stimulated human monocytes and fibroblasts from RA synovial tissues. This effect was most likely mediated via the cyclooxygenase, COX-2, pathway as the expression of the COX-2 gene was also suppressed in these cells. In contrast PGE2 synthesis in U937 cells, which do not express the COX-2 gene, was not suppressed.³⁸

Another herb, *Stephania tetrandra*, has also been used in the treatment of RA.³⁹ An extract from the tuberous root, tetrandrine, has been shown to have inhibitory activity on monocyte production of IL-1, TNF- α , IL-6 and IL-8.³⁶ Additionally, it also suppressed IL-1 activity, lymphocyte IgG secretion, and neutrophil phagocytosis.

In a study of Keishi-bushi-to (KBT), a constituent of five medicinal plants based on Japanese-Chinese TCM (Kampo) prescriptions used to treat RA, the effect of KBT on the development of collagen-induced arthritis (CIA) using the Lewis rat CIA model was examined.⁴⁰ In this model, RA was induced with type II collagen (CII). Oral administration of KBT resulted in a reduction in the severity of the arthritis, especially if it was administered at least 7 days

prior to the induction of arthritis by CII. Plasma IgG and IgM anti-CII antibody levels were lower in KBT-treated rats compared with controls. Moreover, the clearance of IgG anti-CII antibody from circulating blood after intravenous injection was faster in KBT-treated rats.

Atopic Dermatitis

Atopic dermatitis is a common skin disorder which often begins in early infancy, and can persist into adult life as a serious handicap affecting quality of life.⁴¹ The immunological basis of atopic dermatitis involves increased IgE production to a wide range of allergens, accompanied by a predominant Th2 response with increased IL-4 production⁴²⁻⁴⁴ and increased expression of the low-affinity IgE receptor, CD23, on peripheral blood mononuclear cells⁴⁵ and skin Langerhan cells.⁴⁶ Decreased IFN- γ production has been shown to contribute to the increased IgE synthesis seen in these patients.⁴²⁻⁴⁴

Current treatment protocols for severe refractory atopic dermatitis often involve both topical and systemic steroids or cyclosporine.⁴⁷ The herbal decoction, Zemaphyte, contains 10 herbs, namely, *Potentilla chinensis*, *Tribulus terrestris*, *Rehmannia glutinosa*, *Lophatherum gracile*, *Clematis armandii*, *Ledebouriella saseloides*, *Dictamnus dasycarpus*, *Paeonia lactiflora*, *Schizonepeta tenuifolia* and *Glycyrrhiza glabrae*. Zemaphyte has been shown to be efficacious in the treatment of atopic dermatitis in children and adults in 2 rigorous double-blind placebo-controlled trials.^{48,49} Forty-seven children were given either active treatment or placebo for 8 weeks with a 4-week wash-out period.⁴⁸ In the 37 children who completed the study, there was a significant decrease in erythema and surface damage with Zemaphyte. This was confirmed in the later adult study where the median decrease in erythema was 91.4% compared to 10.6% with placebo, and the median decrease in surface damage score was 85.7% compared to 17.3% with placebo.⁴⁹ Further follow-up studies a year later showed that a small proportion of children was able to discontinue therapy,⁵⁰ whereas no adult patients could stop the drug, although half of the adult patients who opted to continue treatment were able to change to an alternate day regimen.⁵¹ Although none of the adult patients showed any evidence of drug toxicity, however, at least 2 children had elevated serum aspartate aminotransferase levels which was reversible once the therapy was discontinued.⁵²

Possible mechanisms of action of these herbs include a dose-dependent inhibition of IL-4 induced expression of the low-affinity IgE receptor, CD23 on monocyte.⁵³⁻⁵⁵ Soluble IL-2 receptor and soluble vascular cell adhesion molecule were also decreased following treatment with Zemaphyte. These findings were corroborated by a subsequent study, which showed that HLA-DR and CD23

expression in antigen-presenting cells demonstrated by skin biopsy, were significantly reduced following treatment with this herbal decoction.⁵⁶

Organ Transplantation

The development of new immunosuppressive agents with a high therapeutic index for solid organ transplantation remains a priority. As an extension of their use in autoimmune diseases, TCM with immunosuppressive properties have been tested in animal models of organ transplantation.

Berberamine, an alkaloid from the plant *Berberis juliane*, has been demonstrated to have anti-hypertensive, anti-arrhythmic and immunosuppressive properties.⁵⁷ Luo and colleagues⁵⁸ showed that berberamine was able to inhibit the lymphoproliferative response to Concanavalin A (Con A) and LPS, decrease the plaque-forming colonies to T-dependent antigen, as well as decrease the CD4+/CD8+ ratio. Moreover, berberamine not only suppressed the mixed lymphocyte reaction (MLR) and delayed-type hypersensitivity reaction (DTH), but was able to prevent rejection of skin grafts in mice.⁵⁹ Berberamine, at concentrations of 25 mg/kg and 50 mg/kg, was able to prolong allograft survival to a median of 15 days and 18 days, respectively, compared to control-treated mice which rejected the skin grafts by a median of 14 days. Cyclosporine had the best treatment effect, with prolongation of skin graft survival to a median of 19 days.

TWHf, which has been used extensively for the treatment of autoimmune diseases in China, has also been studied for its use in organ transplantation.⁶⁰ Demethylzelasteral (TZ-93), a triterpenoid isolated from the root cortex of TWHf, was shown to inhibit the MLR in mice splenic cells.⁶¹ Studies on heart allograft transplant in Lewis rats demonstrated that a combination of TZ-93 at 10 mg/kg/day with cyclosporine increased graft survival to 15.0 ± 1.2 days, whereas single drug treatment with TZ-93 also improved survival to 17.4 ± 2.9 days. On the other hand, untreated control rats rejected their heart allografts after 6 days.

Our laboratory has focused on the immunosuppressive properties of the Chinese herbal decoction, CM, in organ transplantation.⁶² Our earlier studies showed that CMX-13, a hydrophobic extract of CM, suppressed the lymphoproliferative response to phytohaemagglutinin (PHA), decreased expression of PHA-stimulated T-cell activation markers, IL-2 receptor (CD25) and HLA-DR, suppressed PWM-stimulated immunoglobulin synthesis by peripheral blood mononuclear cells, and inhibited the MLR.^{63,64} The Brown Norway $\rightarrow$ Lewis rat lung transplant model is a model of aggressive and rapid allograft rejection in which all grafts are completely destroyed by day 6 post-

transplant. We studied the efficacy of CMX-13 in preventing acute rejection in this model. The stage of acute rejection (AR) was graded by a pathologic intensity score (stages I to IV), based on perivascular and peribronchial mononuclear cell infiltrates, oedema, vasculitis, necrosis, and intra-alveolar haemorrhage.⁶⁵ CMX-13, at a dose of 5 mg given on 3 days, decreased the AR from stages IV to II, and was able to prevent vasculitis, necrosis and haemorrhage, features of the aggressive rejection process (Fig. 2). This effect was similar to that seen with a single high dose cyclosporine given at 25 mg/kg.

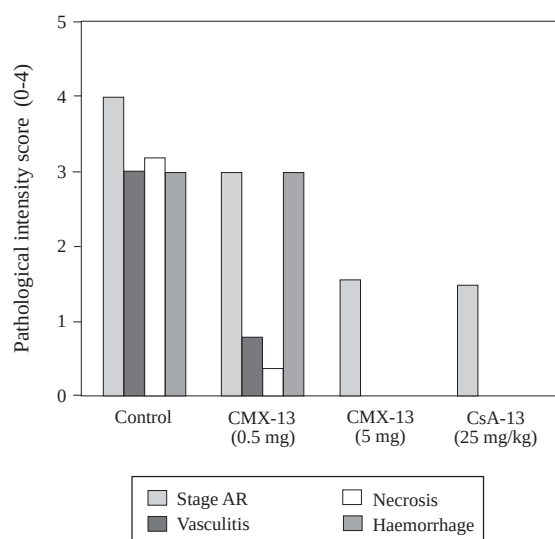


Fig. 2. Effect of CMX-13 on lung allograft in Brown Norway $\rightarrow$ Lewis rats. The stage of acute rejection (AR) was graded by a pathologic intensity score (stages I to IV), which included perivascular and peribronchial mononuclear cell infiltrates, oedema, vasculitis, necrosis, and intra-alveolar haemorrhage.

Conclusion

Although the Chinese philosophy of medical treatment is based on achieving a “perfect balance between the Yin and Yang”, in recent years, the use of TCM as immunosuppressive agents has been studied *in vitro* and *in vivo* in various experimental animal models of autoimmune diseases and allograft transplant. Moreover, experimental studies based on active extracts of several different herbs commonly used as immunosuppressants, have identified a few extracts active in other cytokine-mediated diseases, such as mesangial proliferative glomerulonephritis.⁶⁶ There are, however, very few well-designed randomised placebo-controlled clinical trials demonstrating their use in various diseases.^{48,49} In conclusion, there is both laboratory and clinical evidence that the derivatives of many of these herbs may have significant beneficial immunosuppressive effects, however, concerns of toxicity such as hepatotoxicity, must also be addressed.⁵² This is especially true as the pot-pourri of chemicals produced by these plants are extremely

variable, and may be affected by seasonal changes, agricultural conditions, to name a few. Hence, exact dosing of the active component is difficult in the current TCM prescriptions.

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