Immunomodulation by Chai-Ling-Tang，a formula consisting of twelve Chinese herbs

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Abstract：Chai-Ling-Tang(CLT) is a formula that combines two traditional Chinese herbal medicine prescriptions of Xiao-Chai-Hu-Tang and Wu-Ling-San. The Xiao-Chai-Hu-Tang consists of 7 herbs, which are bupleurum, scutellaria, pinellia, ginger, jujube, ginseng and licorice, and has been suggested to have anti-inflammatory and anti-allergy effects. Wu-Ling-San, which consists of poria, polyporus, alisma, atractylodes, and cinnamon bark, is implied to have diuretic effects. In this paper, the clinical and experimental evidences were reviewed to demonstrate the immunomodulatory effects of CLT. Additionally, some observations that may be due to mechanisms other than immunomodulation were also summarized.
Key words：drugs, Chinese herbal; Chai-Ling-Tang; nephrotic syndrome; immunomodulation

For more than 5000 years, Chinese herbal medicines have helped people live a longer and healthier life. They have been used clinically for over 2500 years, playing a crucial role in traditional Chinese medicine. Chinese medicine practitioners usually prescribe the herbs as certain formulas according to the principles of Yin-Yang, five elements theory and eight diagnostic principles theory in traditional Chinese medicine by analyzing and classifying the information collected from patients. The diagnosis and established therapeutic methods will be used to determine how to combine appropriate herbs for the prevention and treatment of diseases. One of these herbal remedies is Chai-Ling-Tang(CLT), which is a formula that combines two traditional Chinese herbal medicine prescriptions of Xiao-Chai-Hu-Tang and Wu-Ling-San. The Xiao-Chai-Hu-Tang consists of 7 herbs, which are bupleurum, scutellaria, pinellia, ginger, jujube, ginseng and licorice,

and has been suggested to have anti-inflammatory and anti-allergy effects[1]. Wu-Ling-San, which consists of poria, polyporus, alisma, atractylodes, and cinnamon bark, is implied to have diuretic effects. CLT has been used to treat various diseases, especially those that are due to immune dysfunction. These include rheumatoid arthritis[2,3], systemic lupus erythematosus[4], nephrotic syndrome[5 – 10], otitis media[11,12], hearing loss[13,14], idiopathic thrombocytopenic purpura[15], urinary tract fibrosis[16], anemia[17], recurrent abortion[18 – 22], prostatic hyperplasia[23,24], and aqueous flare[25,26]. In recent years CLT has drawn a considerable amount of attention in the scientific community because of its anti-inflammatory, immunomodulatory, and anti-tumor properties[27]. Various studies have been conducted to investigate how CLT affects the immune system.

1　Immunomodulation by CLT：clinical evidence

Clinical evidence has been accumulated to demonstrate that CLT is effective in treating renal diseases. It has been shown that CLT can improve proteinuria in minimal change nephrotic syndrome as well as chronic glomerulonephritis in human. Numerous studies have shown that CLT′s immunomodulatory effects may contribute to its effectiveness in treating renal diseases. In a study by Kimura, *et al*[1]. CLT was administered to four patients with steroid-dependent relapsing nephrotic syndromes(SDNS) in association with prednisolone and immunosuppressive agents. The histological diagnosis showed minimal change in three patients and mild focal glomerulonephritis in the other. After the start of CLT administration the relapse was markedly suppressed in the patients with minimal change nephrotic syndrome but not at all in the patient with focal glomerulonephritis. Thus it appears that CLT is effective for treating steroid-dependent nephrotic syndrome.

In the study by Yoshikawa, *et al*[10] the initial treatment was to determine if CLT could be co-administrated with prednisolone. They found that CLT might prevent subsequent relapses in conjunction with prednisolone. To

further determine whether similar results could be obtained with a combination of only initial 8-week prednisolone and CLT, the effects of such treatment were compared to that of the treatment with 18-week prednisolone and CLT in 196 children with SDNS. They demonstrated that the combination of an initial 8-week prednisolone and 2-year CLT treatment is effective in children with steroid-responsive nephrotic syndrome.

Liu[9] also conducted a clinical study in which 37 children with SDNS were administered CLT with corticosteroid. After treatment with CLT, relapses were markedly controlled, the time for negative conversion of proteinuria shortened, the prednisone dosage significantly reduced, and side effects eased as well. Thirty-two children with SDNS treated with prednisone and cyclophosphamide（an immunosuppressive cytotoxic drug）were served as the control of the study. The results demonstrated that short-term and long-term relapses, and average prednisone dosage were similar between these two groups. It was thus concluded that CLT might be a useful substitute for patients with SDNS who failed to respond to or manifest severe toxic effects from cytotoxic agents.

Idiopathic thrombocytopenic purpura(ITP) is another immune disorder that can be treated with CLT as shown in a study that CLT was used to treat 40 patients with steroid-unresponsive ITP[15]. The mechanism of action of CLT in the treatment of ITP may be related to its modulatory effects on the production of various cytokines. Evans syndrome is a rare disorder characterized by combined ITP and autoimmune hemolytic anemia. A 51-year-old male diagnosed as having Evans syndrome was treated with 25 mg of prednisolone, but his anemia and thrombocytopenia progressed. He was then treated with CLT. Following administration of $9.0 \text{ g} \cdot \text{d}^{-1}$ of CLT granules along with prednisolone, the platelet count increased from 61×10^9 L^{-1} to 123×10^9 L^{-1} after one week, and hemoglobin levels rose from 95 $g \cdot L^{-1}$ to 120 $g \cdot L^{-1}$ after three weeks. The patient maintained a good physical condition after the prednisolone dose was reduced, although Coomb′s test and PAIgG levels remained positive[17]. Thus, CLT seems to be a promising therapeutic agent for steroid-resistant ITP and autoimmune hemolytic anemia, and appears to have no side effects.

CLT has also been used to treat otitis media. A study by Ikeda, et al[11] revealed that CLT might resolve inflammation and immune responses associated with secretory otitis media. In this study, a partial or complete improvement without serious adverse reaction was demonstrated.

While the pathogenesis of steroid-responsive sensorineural hearing loss(SNHL) is still unclear, it is suspected that immune complex disease or vasculitis might be involved. Prednisolone has been used in traditional treatment for SNHL. CLT has, however, achieved beneficial effects in treating SNHL in two studies performed by Kanzaki, et al[13] and O-Uchi, et al[14]. They observed that the combined effects of prednisolone and CLT enabled a decrease in the necessary maintenance dose of prednisolone.

At present two types of immunity-related abortion are recognized. One is caused by autoimmune disorders as exemplified by the antiphospholipid antibody syndrome, in which the T help-1/T help-2（Th1/Th2）balance is excessively shifted to polarization of Th2. The other is caused by alloimmune fetal-maternal disorder, a condition associated with increased serum activity of Th1 cytokines. CLT have been used in the treatment of these immunity-related habitual abortions and were reported to be clinically effective for the type Ⅰ patients. In a study performed by Takakuwa, et al[21], twelve patients who had experienced a total of 27 spontaneous abortions in their previous pregnancies and had no other pregnancy history except for one patient were treated with 9.0 g of CLT per day before their next pregnancy. The positive value of antiphospholipid antibodies was converted to negative in 9 out of 12 patients through the treatment. In 10 out of 12 patients, their new pregnancy continued successfully and delivered offspring（success rate：83.3%）. In another study by Takakuwa, et al[22,24], it has shown that twelve women with antiphospholipid antibodies who had suffered from two or more recurrent spontaneous abortions or fetal deaths had successful pregnancy outcomes after immunosuppressive therapy with CLT. The antiphospholipid antibody titers were determined by enzyme-linked immunosorbent assay against cardiolipin, phosphatidyl serine and phosphatidyl inositol. Plasma levels of 6-ketoprostaglandin F1α （6-ketoPGF1α） and thromboxane B_2 (TXB_2) were determined by radioimmunoassay. All of the 13 pregnancies resulted in term delivery. None of the 13 patients suffered from any pregnancy-induced hypertension, and only one showed intrauterine growth retardation. A significant decrease in antiphospholipid antibody titer was observed after immunosuppressive therapy. The 6-ketoPGF1α/TXB_2 ratios before and after the therapy, and at the 1st, 2nd and 3rd trimesters of pregnancy were 0.62 ± 0.40, 0.88 ± 0.11, 0.84 ± 0.55, 1.25 ± 0.83 and 0.67 ± 0.41, respectively. The ratio at the 2nd trimester was significantly higher than that before the therapy （ $P < 0.05$, paired t-test, $n = 9$ ）. The results indicate that the immunosuppressive therapy affected the physiological balance between thromboxane A_2 and prostacyclin, and improved clinical symptoms such as recurrent fetal wastage.

The alterations of peripheral blood lymphocyte subsets were subsequently analyzed in the patients with recurrent fetal wastage who were treated with CLT for positive antiphospholipid antibodies to elucidate the underlying mechanisms of the therapy. The titer of antiphospholipid antibodies was significantly decreased by CLT at one and two months after commencement of treatment and in the new pregnancies when compared to that before CTL administration. The percentage of CD19$^+$ cells was significantly decreased, while the percentage of CD4$^+$ cells and the CD4/CD8 ratio significantly increased at two months after commencement of CLT treatment and in the new pregnancies when compared to that before CTL administration. Thus, it was suggested that the administration of CLT induce the predominance of CD4$^+$ cells in conjunction with the suppression of antiphospholipid antibodies. Moreover, the suppression of CD19$^+$ cells (B cells) was induced by the administration of CLT, which might be responsible for the successful continuation of pregnancy in the patients[24]. The clinical effect of these herbal medicines can be explained by how they function in the maternal immune system. The CLT enhances Th1 cytokine (tumor necrosis factor-α and interferon-γ) release from peripheral blood mononuclear cells and may suppress the production of autoantibodies from B cells. However, CLT does not affect cytokine release from decidual mononuclear cells, which are directly in contact with fetal trophoblasts. These herbal medicines do not enhance the killer activity of decidual mononuclear cells. Thus, the differential effects of CLT on the release of Th1/Th2 cytokines from peripheral blood mononuclear cells and decidual mononuclear cells may be responsible for the efficacy of these medicines in the treatment of autoimmunity-related habitual abortion[20]. Therefore CLT may have therapeutic potential, particularly in autoimmunity-related recurrent abortion in which Th2 response is pathologically enhanced, but not in recurrent abortion involving alloimmune fetomaternal derangement, a condition of an enhanced Th1 response[18,19].

2　Immunomodulation by CLT: experimental evidence

Some laboratory studies also indicated CLT has anti-inflammatory and immune modulatory effects. A study conducted by Nagata, *et al*[28] has demonstrated that CLT can moeulate intraglomerular cell-mediated immunity. In this study, the number of intrarenal major histocompatibility complex class (MHC) Ⅱ positive cells and T cells in nephrotoxic nephritis in rats was quantified in order to determine the effect of CLT on immune related glomerulonephritis. Using light microscopy, they found that treatment with CLT suppressed glomerular inflammation such as endocapillary proliferative lesions and mesangial expansion, as compared to the control group. Histological improvement was also found in rats treated with both methylprednisolone and CLT. CLT suppressed infiltrations of intraglomerular MHC Ⅱ positive cells and T cells on the 7th and 14th day after the treatment. Remarkable suppression of T cell infiltration was also noted in rats treated with methylprednisolone along with CLT on the 14th day.

CLT is well known for improving the symptoms of rheumatoid arthritis and other collagen diseases. However, its immunosuppressive effects on autoimmune cutaneous phenomena are not completely understood. A study investigated the effects of CLT on the development of lupus dermatoses in autoimmune-prone MRL/Mp-lpr/lpr (MRL/lpr) mice, an animal model that spontaneously develops skin lesions similar to those seen in human lupus erythematosus. Virgin female MRL/lpr mice at 1 month of age, which were treated orally with CLT, had reduced amounts of IgG deposition at the dermoepidermal junction, titers of anti-DNA antibodies and rheumatoid factor, and lymphoproliferauion[2]. These results support the use of traditional herbal medicines in the patients with human rheumatoid arthritis and systemic lupus erythematosus.

Ito, *et al*[6] investigated the immunological changes of skin, kidney, spleen cells and serum in autoimmune-prone MRL/lpr, MRL/n and C57BL/6J mice that had been treated with CLT. In MRL/lpr mice treated with CLT, the improvement of proteinuria, reduction in the number of hematoxylin bodies in kidney, and reduced serum levels of blood urea nitrogen were observed. These results indicated that CLT could inhibit the progression of lupus nephritis. The percentage of CD19$^+$ B cells and the serum levels of IgG$_1$, which is one of the pathogenic factors of lupus dermatoses and lupus nephritis, were significantly reduced in CLT-treated MRL/lpr mice. Therefore, it was suspected that the B cell function was suppressed by CLT. In addition, CD4/CD8 ratio in spleen and lymphoproliferation in MRL/lpr mice were also decreased. Interestingly, interleukin-4-producing spleen cells were increased significantly as examined by enzyme-linked ImmunoSPOT assay, whereas interferon-γ mRNA expressions were reduced in CLT-treated MRL/lpr mice. Regarding the Th1/Th2 balance, an imbalance towards Th1 predominance may play a significant role in the pathogenesis of MRL/lpr mice, and the Th1 axis was suppressed and the Th2 axis became predominant in CLT-treated MRL/lpr mice. On the other hand, Th2 type immunoglobulins (IgG$_1$) were suppressed. These results suggested that the CLT have a potential to repair the shifted Th1/Th2 balance and hypergammaglobulinemia, resulting in therapeu-

tic effects.

Immunomodulatory and anti-tumor activities of CLT were also investigated in another study. Oral administration of CLT into mice augmented the antibody response to 2, 4, 6-trinitrophenyl-haptenated sheep red blood cells no matter whether the antigens were given intraperitoneally or orally[27]. In addition, orally administered CLT markedly enhanced the phagocytic and lysosomal enzyme activities of the peritoneal macrophages. Furthermore, a significant inhibition of tumor growth was observed in a syngeneic tumor-mouse system when CLT was administered orally. These results suggest that CLT function as an oral adjuvant or an oral biological response modifier.

3　Mechanisms other than immunomodulation by CLT

In addition to immune modulation, there is also evidence that CLT may have other functions contributing to its clinical efficacy. In the patients with polycyctic ovary syndrome (PCOS), CLT administration appeared to have a steroidal effect in anovulatory PCOS patients. As a result of the treatment, serum luteinizing hormone and the luteinizing hormone/follicle-stimulating hormone ratio significantly decreased, and the ovulatory rate was increased 70.6%[28]. Serum testosterone levels were within normal limits before the treatment, and did not significantly change during the treatment. CLT may therefore be useful for the treatment of anovulation in PCOS patients.

Effects of CLT were also examined in a rat model with renal complications. Thirteen weeks after subtotal nephrectomy, the blood pressures in rats given CLT were lower than those without CLT. The urinary protein excretions and glomerular sclerosis were markedly decreased in the CLT-treated rats. Arteriolar diameters were measured using microvascular casts. Both the afferent and efferent arterioles were significantly dilated, however, the efferent arterioles in CLT rats being dilated to a greater extent than that of the afferent[8]. These results indicated that CLT lessened renal damages in the rat subtotal nephrectomy model, possibly through blood pressure reduction and the efferent arteriolar dilatation.

To investigate the effectiveness of CLT on nephrosis and elucidate its mechanism of action, Joarder, et al[29] made a puromycin aminonucleoside (PAN) rat model by a single intra-peritoneal injection of PAN at a dose of 100 mg·kg^{-1} and compared it to the normal control. CLT was administered at various dose levels (100, 200, 500 mg·kg^{-1}) orally for 8 days after the initial injection of PAN. The results support the hypothesis that CLT has enhancing effects on the superoxide dismutase-like activity and on the synthesis of prostanoid in PAN-induced nephrosis,

and that these effects are responsible for the mechanism of action of CLT.

Gentamicin has nephrotoxicity that can impair renal function. A study showed that CLT worked against gentamicin toxicity in gentamicin nephrotoxicity rat models. CLT administration reduced the increased excretion of urinary N-acetyl-β-D-glucosaminidase and proteins, and decreased creatinine clearance induced by gentamicin. Gentamicin increased renal cortical malondialdehyde concentration in normal diet group but not in the CLT diet group[30]. The renal cortical gentamicin concentration was not different between the two groups. Thus, CLT exhibited protective effect against gentamicin nephrotoxicity, possibly through its anti-oxidant action.

The effects of CLT on monoclonal antibody (mAb) induced proteinuria were examined by Kawachi, et al[31]. Significant reduction of proteinuria by CLT treatment was observed. No significant difference was recognized between the total amount of mAb bound to glomeruli at 1 h after mAb injection in CLT-treated and non-treated rats, indicating that CLT pretreatment has no effects on the number or quality of antigenic molecules. It was thus concluded that mAb-induced proteinuria in rats is significantly suppressed by CLT.

Effects of CLT on passive Heymann nephritis in rats, a model similar to human membranous nephropathy, were examined. It was found that the excretion of urinary protein was significantly suppressed in the CLT-treated group as compared to that in the phosphate buffered saline control group at 15 d after anti-FxlA antibody injection. The decrease in serum albumin and total protein and the increase in total serum cholesterol were significantly inhibited in the CLT-treated group when compared to the control group. The result suggested that proteinuria in passive Heymann nephritis be significantly suppressed by CLT[32].

Otitis media with effusion (OME) is often recurrent and even become chronic. There is now considerable experimental and clinical evidence that the cilia in the tubotympanum play an important part in the prevention of OME. CLT has been shown to stimulate the ciliary activity in vitro, and oral administration of the medicines also stimulated the ciliary activity in the tubotympanum rather than physiological states[33]. A study was designed to investigate whether oral administration of CLT could prevent experimental OME in the guinea pig. The ciliary activity in the tubotympanum was significantly reduced in the low-dose groups (120 mg·kg^{-1}) when compared to the normal-control group. In contrast, the magnitude of reduction in ciliary activity was much smaller in the high-dose group (600 mg·kg^{-1}). The ciliary activity especially in

the Eustachian tube and the middle ear close to the tympanic orifice at 3 and 7 d in the high-dosage group was not significantly different from that in the normal-control group. Mucociliary clearance time in the high-dosage group was not different from that in the normal-control group throughout the observation period. The groups treated with CLT, especially the high-dose group, exhibited much milder pathological changes in the tubotympanum than did the saline-control group. In conclusion, clinical application of CLT could be an effective measure to prevent the occurrence of OME and also the recurrence of the disease, especially OME-prone individuals.

Hattori, *et al*[34] investigated the components of CLT. The study was intended to find which one of the twelve herbs might be responsible for the antinephritic action that CLT exhibits. It was found that the antinephritic action of CLT, resulting from the inhibition of endothelin-1 production, might be attributed to the alisols in Ze-Xie (Alismatis rhizoma). There is also evidence to indicate that the antinephritic action of CLT may be partially due to inhibition of adhesion molecule expression in the glomeruli. The Xiao-Chai-Hu-Tang and CLT consisting of similar herbal prescriptions contain glycyrrhizin, which is a strong inhibitor of 11 β-hydroxysteroid dehydrogenase. Cross over open trials were conducted in healthy subjects to clarify prednisolone pharmacokinetics after co-administration of these preparations. The results were expressed as ratios of endogenous cortisone to cortisol. Because of the equal glycyrrhizin content in all three preparations, it was unexpected that the 11 β-hydroxysteroid dehydrogenase effect was different amongst the three groups. These observations suggest that some unknown metabolic enzyme modifiers, promoters or inhibitors, be involved in these traditional treatments[35].

In conclusion, through these series of studies, CLT has demonstrated its potential of promoting the steroidal effects in treating immune disorders, stimulating the pituitary gland to increase the secretion of ACTH, inhibiting the metabolism of corticosteroids, and enhancing the effects of the immunosupression agent. Furthermore, CTL may be by itself immunomodulatory. On the current market, conventional treatments for various diseases and disorders are often ineffective and complicate or nonspecific, and many carry with them undesirable side effects that by using CLT instead we may hope to avoid. Although more studies are imperative to examine the accuracy of these former results, Chai-Ling-Tang may be the answer to a much-sought-for remedy for the above stated disorders and medical conditions. Regardless of the need for further research, CLT has at least opened a new horizon for treating these autoimmune or systemic diseases — the horizon of

alternative medicine or traditional Chinese medicine therapy.

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柴苓汤的免疫调节作用

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摘要：柴苓汤是由两个传统中药方剂小柴胡汤和五苓散所组成。小柴胡汤包含有 7 味中草药即柴胡、黄芩、半夏、生姜、大枣、人参和甘草。长期以来被认为具有消炎，抗过敏作用，并被广泛应用于临床实践中。五苓散由茯苓、猪苓、泽泻、白术和桂枝 5 味中草药组成，是临床上具有代表性的消肿利水方剂。本文概述了柴苓汤的免疫调节作用和一系列的临床试验观察研究，并且总结了除免疫作用机制以外的有关柴苓汤的作用机制观察。

关键词：中草药；柴苓汤；肾变病综合征；免疫调节

（本文编辑　董立春）