Traditional Chinese Herbal Medicine and Lupus Nephritis

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Abstract

Available treatments for lupus nephritis, a potentially fatal autoimmune disease, are limited by suboptimal efficacy and increased risk of infections and malignancies; inevitably they do not meet clinical demands. Traditional Chinese herbal medicine has recently been recognized for its potential therapeutic benefits for lupus nephritis. Encouraging evidence from clinical trials and observational studies demonstrate that Chinese herbal medicine may possess benefits for treating patients with lupus nephritis. The significant benefits of these herbal medicine modalities that have been observed and reported include improving clinical efficacy, reducing level of antibodies and proteinuria, ameliorating renal damage, diminishing the dosage of prednisone use as well as decreasing toxicity, and preventing disease flare-up. This overview aggregates the current body of medical knowledge on the therapeutic benefits of several types of Chinese herbal medicines for lupus nephritis, and these promising herbal medicines may challenge the current treatment paradigms available for lupus nephritis and inform future research and clinical practice.

Keywords: Chinese herbal medicine; Lupus nephritis; Rhizoma alismatis

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with potential lethality which is incurable and requires long-term treatment [1]. Lupus nephritis, which occurs in 38%-60% of SLE patients during the course of the disease, results in significant morbidity and mortality [2,3]. SLE patients who develop lupus nephritis have a reduced life expectancy by 15 years and suffer poor health-related quality of life [2,4,5]. The rate of progression to end-stage renal disease remains high [6-8]. Current therapeutic approaches cannot meet the clinical demands of patients who have lupus nephritis and are limited by suboptimal efficacy of the treatment and increased risk of infections. Several novel biologic agents for lupus nephritis also show substantial toxicity, and the results of long-term application remain unknown [9-11]. Given the complexity, cost and apparent ineffectiveness of the therapeutic armamentarium used in lupus nephritis, complementary and integrative therapies are becoming increasingly attractive [12,13]. Chinese herbal medicine, which has been practiced for thousands of years, is still one of the main treatments in China and eastern Asia and continues to be disseminated widely around the world in the 21st century. After millennia of use and research, traditional Chinese herbal medicine has recently been recognized for its potential therapeutic benefits for patients with lupus nephritis. Clinical trials and observational studies provide encouraging evidence that Chinese herbal medicine possesses benefits for patients with lupus nephritis [14,15]. Significant benefits of Chinese herbal modalities that have been observed and reported include improving symptoms, reducing level of antibodies and proteinuria, ameliorating renal damage, diminishing the dosage of prednisone use as well as decreasing toxicity, and preventing disease flare-up [14,16,17].

In this review, we have conducted a comprehensive search of four English and Chinese biomedical databases and from inception through February 2018. These databases included PubMed, Chinese National Knowledge Infrastructure, Chongqing VIP, and WanFang Med Online. Searches were limited to human studies in English and Chinese language. We also screened the reference lists of selected studies for additional publications. Studies were grouped into the four categories which include 15 randomized controlled trials of Chinese herbal medicine for lupus nephritis (Table 1). In all these studies, participants met 1982 or 1997 ACR criteria for classification of lupus nephritis. This overview summarizes the current body of knowledge on the therapeutic benefits of several types of Chinese herbal medicines for lupus nephritis. These promising herbal medicines may challenge the current treatment paradigms available for lupus nephritis and inform future research and clinical practice.

Liu-wei-di-huang pill for lupus nephritis

Use of the Liu-wei-di-huang pill, among the most popular Chinese herbal medicines for chronic kidney disease, was initially recorded in the earliest Chinese pediatric monograph, Key to Therapeutics of Children’s Diseases, during the Northern Song Dynasty (960-1127 AD) [18,19]. The pill is composed of six species of medical herbs: Radix Rehmanniae Praeparata, Rhizoma Dioscoreae, Fructus Corni, Cortex Moutan, Poria and Rhizoma Alismatis. According to traditional Chinese medicine and western medicine theory, the pill is believed to have the function of ‘nourishing kidney yin’ and is also suggested to have anti-inflammatory and immunomodulation effects to protect kidney function [20-22].

We identified four randomized controlled trials of Liu-wei-di-huang, which comprised a total of 307 patients [23-26]. The mean age ranged from 22 to 25 years, and disease duration was 29.5-44.4 months. Average study duration was 3 to 6 months. One randomized controlled study of 33 patients with lupus nephritis administered the Liu-wei-di-huang pill (3 g, three times a day) combined with prednisone 7.5 mg/d-60 mg/d and cyclophosphamide 8-12 mg/kg via intravenous injection once every 2-4 weeks [23]. 31 patients in the control group were given prednisone and cyclophosphamide (same dosage). Compared with the...
<table>
<thead>
<tr>
<th>Source [Ref]</th>
<th>Number (Female %)</th>
<th>Mean Age (year)</th>
<th>Disease Duration (months)</th>
<th>Intervention</th>
<th>Control</th>
<th>Study Duration</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Liu-wei-di-huang pill</strong></td>
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<tr>
<td>Zheng, [23]</td>
<td>64 (90.6%)</td>
<td>24</td>
<td>44.4</td>
<td>Liu-wei-di-huang pill, 3 g three times a day; Cyclophosphamide, 8-12 mg/kg, intravenous injection every 2-4 weeks; Prednisone, 7.5 mg/d-60 mg/d/gd.</td>
<td>Cyclophosphamide, 8-12 mg/kg, intravenous injection every 2-4 weeks; Prednisone, 7.5 mg/d-60 mg/d.</td>
<td>3 months</td>
<td>↓ 24 h urine protein, ESR s ↑ C3, Alb s ↓ Scr ns Adverse effects, recurrence rate s</td>
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<tr>
<td>Huang, [24]</td>
<td>51 (45.1%)</td>
<td>22</td>
<td>38.4</td>
<td>Liu-wei-di-huang pill, 3 g, three times a day; Mycophenolate mofetil, 0.5 g/d/2.0 g/d; Prednisone, 7.5 mg/d-60 mg/d.</td>
<td>Mycophenolate mofetil, 0.5 g/d/2.0 g/d; Prednisone, 7.5 mg/d-60 mg/d.</td>
<td>3 months</td>
<td>↓ 24 h urine protein s ↑ C3, Alb s ↓ Scr ns Adverse effects s</td>
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<tr>
<td><strong>Xian, [25]</strong></td>
<td>120 (NR)</td>
<td>29.5</td>
<td></td>
<td>Liu-wei-di-huang decoction, 200 ml; twice a day; Tripterygium glycosides tablet, 20 mg, three times a day; Cyclophosphamide, 0.4 mg intravenous injection every 2-4 weeks; Prednisone, 7.5 mg/d-1.2 mg/kg/d.</td>
<td>Cyclophosphamide, 0.4 g, intravenous injection every 2-4 weeks; Prednisone, 7.5 mg/d-1.2 mg/kg/d.</td>
<td>6 months</td>
<td>↓ 24 h urine protein, ESR s dsDNA, ANA s SLEDAI s Scr ns Adverse effects ns</td>
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<tr>
<td><strong>Bai, [26]</strong></td>
<td>72 (87.5%)</td>
<td>25</td>
<td>33.9</td>
<td>Liu-wei-di-huang decoction, 200 ml, twice a day; Tripterygium glycosides 0.6 g/1.0 g, intravenous injection every 4 weeks; Prednisone, 7.5 mg/d-1 mg/kg/d.</td>
<td>Tripterygium glycosides tablet, 0.6 g/1.0 g, intravenous injection every 4 weeks; Prednisone, 7.5 mg/d-1 mg/kg/d.</td>
<td>6 months</td>
<td>↓ 24 h urine protein, Scr s ↑ C3, Alb s ↑ ESR s Adverse effects s</td>
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<td><strong>Artemisinins</strong></td>
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<td>Lu, [31]</td>
<td>61 (93%)</td>
<td>44</td>
<td>4.3</td>
<td>Artemisinin powder, 0.2 g, three times a day; Cordyceps powder, 1 g, three times a day.</td>
<td>Tripterygium glycosides tablet, 1 mg/kg/d; Baoshenkang tablet, 150 mg, three times a day.</td>
<td>36 months</td>
<td>↓ 24 h urine protein, Scr, BUN s ↑ C3, Alb, Ccr s ↑ β2-MG ns</td>
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<tr>
<td>Huang, [32]</td>
<td>60 (92%)</td>
<td>29</td>
<td>46</td>
<td>Class I/class II, Artesunate tablet, 25 mg, twice a day; Class I: Artesunate tablet, 25 mg, twice a day, and prednisone 0.5 mg/kg/d.</td>
<td>class I/class II: Tripterygium glycosides tablet, 10 mg, three times a day; class III: Tripterygium glycosides tablet, 10 mg, three times a day, and prednisone 0.5 mg/kg/d.</td>
<td>2 months</td>
<td>↓ 24 h urine protein, ESR, CD8+ s ↑ C4, IL-2 s ↑ C3 ns ↑ IgG, ds-DNA ns CD3+, CD4+ ns</td>
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<tr>
<td><strong>Cordyceps sinensis</strong></td>
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<tr>
<td>Wang, [35]</td>
<td>118 (83%)</td>
<td>31</td>
<td>21.3</td>
<td>Cordyceps sinensis capsule, 1.0 g, three times a day; Tacrolimus capsule, the first dose of 0.05 mg/kg, twice a day for 3 days, then maintain the blood concentration at 5-15 ug/L.</td>
<td>Tacrolimus capsule, the first dose of 0.05 mg/kg, twice a day for 3 days, then maintain the blood concentration at 5-15 ug/L.</td>
<td>12 months</td>
<td>↓ 24 h urine protein, urine RBC s ↑ C3, Alb s ↑ SLEDAI s Scr, dsDNA ns Adverse effects s</td>
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<tr>
<td>Zhu, [36]</td>
<td>120 (89%)</td>
<td>50</td>
<td>NR</td>
<td>Cordyceps sinensis capsule, 1.0 g, three times a day; Cyclophosphamide, 0.5-1.0 g/m2, intravenous injection every 3-4 weeks; Prednisolone, 0.5-1 mg/kg/d.</td>
<td>Cyclophosphamide, 0.5-1.0 g/m2, intravenous injection every 3-4 weeks; Prednisolone, 0.5-1 mg/kg/d.</td>
<td>12 months</td>
<td>↓ 24 h urine protein, urine RBC s ↑ C3, Alb, IL-2 s ↑ SLEDAI s Scr, dsDNA, ANA ns Infection rate s Adverse effects ns</td>
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<tr>
<td>Yang, [37]</td>
<td>136 (84%)</td>
<td>51</td>
<td>NR</td>
<td>Cordyceps sinensis capsule, 1.0 g, three times a day; Cyclophosphamide, 0.5-1.0 g/m2, intravenous injection every 3-4 weeks; Prednisolone, 0.5-1 mg/kg/d.</td>
<td>Cyclophosphamide, 0.5-1.0 g/m2, intravenous injection every 3-4 weeks; Prednisolone, 0.5-1 mg/kg/d.</td>
<td>12 months</td>
<td>↓ 24 h urine protein, urine RBC s ↑ C3, Alb s ↑ SLEDAI s Scr, dsDNA, ANA ns Infection rate s Adverse effects ns</td>
</tr>
<tr>
<td>He, [38]</td>
<td>41 (87.8%)</td>
<td>31</td>
<td>11.4</td>
<td>Cordyceps sinensis capsule, 1.0 g, three times a day; Low molecular heparin, 5000U, hypodermic injection once a day; Prednisolone, 1 mg/kg/d.</td>
<td>Low molecular heparin, 5000U, hypodermic injection once a day; Prednisolone, 1 mg/kg/d.</td>
<td>2 months</td>
<td>↓ 24 h urine protein, Scr, BUN s ↑ Alb s Adverse effects ns</td>
</tr>
<tr>
<td>Li, [39]</td>
<td>50 (90%)</td>
<td>38</td>
<td>82</td>
<td>Cordyceps sinensis capsule, 1.65 g, three times a day; Prednisone, 1 mg/kg/d.</td>
<td>Prednisone, 1 mg/kg/d.</td>
<td>2 months</td>
<td>↓ 24 h urine protein, ESR, CD8+ s ↑ C3, C4, CD4+ s SLEDAI s Ccr ns dsDNA, sIL-2R, CD3+ ns</td>
</tr>
<tr>
<td>Wu, [40]</td>
<td>42 (66.7%)</td>
<td>34</td>
<td>53.5</td>
<td>Cordyceps sinensis capsule, 1.0 g, three times a day; Prednisolone, 1 mg/kg/d.</td>
<td>Prednisolone, 1 mg/kg/d.</td>
<td>2 months</td>
<td>↓ 24 h urine protein, Scr, BUN s dsDNA s C3 s</td>
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</table>

**Tripterygium glycosides**
control group, the Liu-wei-di-huang pill interventions significantly improved 24-hour proteinuria, erythrocyte sedimentation rate, and complement 3 and plasma albumin levels. Notably, the recurrence rate of the treatment group was significantly lower than that of the control group within a year of follow-up. Similar results were found in another study of 51 lupus nephritis patients given the Liu-wei-di-huang pill (3 g, three times a day) combined with prednisone (7.5 mg/d-60 mg/d) and mycophenolate mofetil (0.5 g/d-2.0 g/d) [24]. In addition, the study found that Liu-wei-di-huang pill therapy could significantly reduce the occurrence of adverse effects, such as diarrhea, adiposity, liver damage, infection, and leukocyte descent. The other two RCTs treated participants with 6-month Liu-wei-di-huang decoction, combined with prednisone and cyclophosphamide, and found that Liu-wei-di-huang decoction reduced 24-hour urine protein, decreased serum creatinine level, and improved disease activity scores [25,26]. These clinical studies indicate that Liu-wei-di-huang formulation combined with western medicine has better efficacy with fewer adverse events compared to western medicine alone.

Artemisinins for lupus nephritis

Artemisinin family drugs are extracted from the plant Artemisia annua L. (qing hao), a traditional Chinese herbal medicine that has been used to treat malaria for more than two thousand years in China [27]. Recently, it has been found that artemisinin family drugs also have anti-inflammatory [28] and complex immunosuppressive effects [29]. Artemisinin derivatives show therapeutic effects for SLE, similar to other anti-malarial drugs such as hydroxychloroquine and chloroquine [30]. Two unique randomized controlled trials of artemisinins were identified for lupus nephritis. The course of treatment ranged from 8 weeks to three years. One randomized study of 61 patients with inactive lupus nephritis randomly assigned participants into two groups, each receiving three years of treatment. Artemisinin (0.2 g, three times a day) and cordyceps sinensis were given to the treatment group, and tripterygium glycosides tablets and Bao Shen Kang tablets were given to the control group. Compared to the control group, the treatment group showed significant improvement after treatment in 24-hour urine protein content, creatinine clearance rate and level of complement 3. The study concluded that artemisinin and cordyceps sinensis may delay the recurrence of lupus nephritis, protect renal function and improve the quality of life of patients with lupus nephritis [31]. Similar findings of improvement in renal function and the immune system from artemusate were reported in another randomized controlled study of 60 lupus nephritis patients [32]. Together, artemisinin derivatives may decrease antibody and creatinine levels, erythrocyte sedimentation rate, and urinary protein, as well as improve the level of complement, whether the affected patient has class I, II, or III lupus nephritis. Overall, the clinical studies demonstrate that artemisinins have the potential to preserve kidney health in patients with lupus nephritis. Long term application of artemisinins may also alleviate renal lesions and prevent the recurrence of lupus nephritis.

Cordyceps sinensis for lupus nephritis

Cordyceps sinensis has been known to have the function of 'strengthening kidney and lung, enhancing vigor and vitality' in traditional Chinese medicine theory. It has been suggested that Cordyceps sinensis can regulate the immune system bidirectionally, reduce renal tubulointerstitial damage, inhibit renal fibrosis and improve kidney function [33,34]. Six RCTs totaling 507 patients tested the effects of Cordyceps sinensis on lupus nephritis [35-40]. The treatment duration ranged from 2 to 12 months. Patients in the control groups received glucocorticoid (methylprednisolone or prednisone) and immunosuppressive agents (cyclophosphamide or tacrolimus), while the treatment groups received Cordyceps sinensis preparation (1 g or 1.65 g, three times a day) and the same dose of western medicine. Compared with western medicine controls, the combination treatment of Cordyceps sinensis preparation significantly improved clinical symptoms and disease activity scores, and decreased 24-hour urine protein, anti-ds DNA antibody and serum creatinine levels. Furthermore, the infection and adverse reaction rates in the treatment group were significantly lower than those in the control group. Therefore, Cordyceps sinensis may have a potential role in improving the immune function of patients with lupus nephritis, and have potential clinical therapeutic effectiveness when combined with western medication.

Tripterygium glycosides for lupus nephritis

In Chinese herbal medicine, the extract of Tripterygium wilfordii Hook. f. roots, named Tripterygium glycosides, has been widely used to treat autoimmune diseases including lupus nephritis [41-43]. Several randomized controlled trials have examined the therapeutic effects of Tripterygium Glycosides in patients with lupus nephritis. The results of these studies showed the effects of Tripterygium glycosides (20 mg, three times a day) were similar to the effects of leflunomide (20 mg, once a day) and azathioprine (1-2 mg/kg once a day). Overall, adverse effects due to the use of Tripterygium glycoside did not increase except for incidence of menstrual disorder. Thus, Tripterygium glycosides have therapeutic potential in patients with lupus nephritis, but the signs of menstrual disorder should be monitored during use.

<table>
<thead>
<tr>
<th>Dai, [41]</th>
<th>91 (89%)</th>
<th>NR</th>
<th>NR</th>
<th>Tripterygium glycosides, 20 mg, three times a day; Prednisone, 0.8 mg/kg/d.</th>
<th>6 months</th>
<th>24 h urine protein, Scr ns ↑ C3, Alb ns ↑ Prednisone, 10 mg, three times a day.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong, [42]</td>
<td>82 (74.4%)</td>
<td>25.6</td>
<td>Tripterygium glycosides, 0.5 mg/kg, three times a day; Prednisone, 10 mg, three times a day.</td>
<td>3 months</td>
<td>24 h urine protein, dsDNA s ↑ Platelet, C3, C4 s Adverse effects ns</td>
<td></td>
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<tr>
<td>Wang, [43]</td>
<td>84 (95.2%)</td>
<td>NR</td>
<td>Tripterygium glycosides, 20 mg, twice or three times a day; Prednisone, 10 mg, once a day.</td>
<td>24 months</td>
<td>24 h urine protein, Scr ns ↑ Alb ns s Adverse effects, infection rate ns Menstrual disorder s</td>
<td></td>
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</tbody>
</table>

Table 1 Randomized controlled trials of chinese herbal medicine for lupus nephritis.

Ref= reference; NR=no relevant; s= significant; ns= no significant; Alb= albumin; BUN=blood urea nitrogen; C3=complement 3; C4=complement 4; CCr=creatinine clearance rate; ESR=erythrocyte sedimentation rate; Scr= serum creatinine; SLEDAI=systemic lupus erythematosus disease activity index.
In summary, lupus nephritis remains a therapeutically challenging chronic condition to manage. While evidence regarding the use of traditional Chinese herbal medicine modalities for lupus nephritis remains limited, the data outlined above suggest that Chinese herbal medicine may have synergistic effect with western medicine. The potential therapeutic benefits of certain Chinese herbal medicines may challenge the current treatment paradigms available for lupus nephritis and warrant a new strategy to include Chinese herbal medicine.

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Reference


