Intensive research on the prospective use of complementary and alternative medicine to treat systemic lupus erythematosus

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ABSTRACT: Traditional Chinese medicine has gained increasing acceptance worldwide as a form of complementary and alternative medicine and has been used to treat systemic lupus erythematosus (SLE) inside and outside of China. Herbal medicines are generally low in cost, plentiful, and cause very little toxicity or few adverse reactions in clinical practice. However, the mechanisms by which traditional Chinese medicine treats SLE remain unclear. The immunosuppressive properties of traditional Chinese medicines and/or immunomodulation by those medicines could play an important role in their treatment of SLE.

Keywords: Systemic lupus erythematosus, traditional Chinese medicine, immunity, integrative treatment

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by autoantibody production, complement activation, immune complex deposition, and lymphocyte proliferation that cause tissue and organ damage (1). SLE treatment is individualized and depends on manifestation of symptoms, organ involvement, and disease severity. Antimalarials and nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in the treatment of mild symptoms. Oral corticosteroids and cytotoxic agents are used to treat more severe disease. Other medications (cyclophosphamide, immunosuppressive agents, and tacrolimus) may be used depending on the severity of disease and organ systems involved. Belimumab is approved for use in patients with mild to moderate disease currently taking standard therapy (2). Even so, the treatment of SLE remains a challenge today, particularly in terms of controlling the underlying disease process while at the same time preventing adverse reactions to therapy.

Western medicines such as glucocorticoids and immunosuppressants are used to suppress active immune responses, though this is only a temporary solution. However, long-term use of glucocorticoids and/or high-dose pulse therapy with immunosuppressants often leads to adverse reactions. Traditional Chinese medicine (TCM) focuses on the overall regulation of immune function by reconstructing a stable state, and it seeks to regulate Yin and Yang, Qi and blood and the function of Zang Fu internal organs by enhancing the body's defensive capabilities, improving immune function, and limiting adverse reactions. The other major principle of TCM is an emphasis on individual therapy. The diagnosis and treatment strategy may different substantially for different patients with the same type of SLE. This is called the principle of "treatment based on differentiation of symptom patterns".

2. SLE from the viewpoint of TCM

TCM views SLE as a systemic disease associated with the state of the entire body. According to TCM theory, SLE is caused by imbalances between endogenous physical conditions within the body and exogenous pathogenic factors. Those pathogenic factors for SLE, in Chinese medicine terms, include exuberant heat and toxins, a yin deficiency and interior heat, a yang deficiency in the spleen and kidney, and a qi-yin deficiency. These factors strike when a person is in a weak physical condition, without the strength to resist.

3. Possible mechanisms by which TCM treats SLE

SLE is an autoimmune disease. The immunological indicators differ due to different symptoms in patients (3). Many different types of herbal medicines are used to treat SLE, but few of those medicines have undergone randomized controlled trials. Each therapeutic strategy differs based on the differentiation of symptom patterns. Table 1 shows examples of compounds or extracts derived from traditional Chinese herbal medicines used to treat
Table 1. Examples of compounds or extracts derived from traditional Chinese medicine being used to treat SLE

<table>
<thead>
<tr>
<th>Main TCM herbs</th>
<th>Active component</th>
<th>In vitro and/or in vivo system</th>
<th>Target molecules and pathways</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moutan Cortex</td>
<td>Paeonol</td>
<td>Rat</td>
<td>Reduces levels of TNF-α, IL-1β, and IL-6.</td>
<td>9</td>
</tr>
<tr>
<td>Moutan Cortex</td>
<td>Extracts</td>
<td>Human basophils (KU812 cells)</td>
<td>Suppresses the expression of ICAM-1 and the release of CCL2, CCL5, CXCL8, and IL-6.</td>
<td>10</td>
</tr>
<tr>
<td>Moutan Cortex</td>
<td>Extract containing paeonol and paeoniflorin</td>
<td>Human gingival fibroblasts</td>
<td>Inhibits activation of various inflammation-related genes.</td>
<td>11</td>
</tr>
<tr>
<td>Moutan Cortex</td>
<td>Extracts</td>
<td>Mouse model of type II collagen-induced arthritis (CIA)</td>
<td>Improves the clinical arthritis index, ameliorates the histological deformation of joints, decreases serum levels of rheumatoid arthritis biomarkers, and attenuates Th1-related responses. Suppresses the production of MMPs, TNF-α, IL-1β, IL-6, and chemokines. Suppresses the activation of NF-κB and AP-1.</td>
<td>12</td>
</tr>
<tr>
<td>Moutan Cortex</td>
<td>Spray-dried moutan cortex extract</td>
<td>Mouse peritoneal macrophage</td>
<td>Inhibits the expression of iNOS and TNF-α release. Blocks the activation of NF-κB.</td>
<td>13</td>
</tr>
<tr>
<td>Radix Rehmanniae</td>
<td>Extracts</td>
<td>NC/Nga mice</td>
<td>Reduces the total number of mast cells, CCR3(+) eosinophil immunoreaction, and total serum levels of IgE, IL-2, and IL-4.</td>
<td>14</td>
</tr>
<tr>
<td>Radix Rehmanniae</td>
<td>Rehmanniae polysaccharides</td>
<td>Ultraviolet B (UVB) ray treated mice</td>
<td>Increases serum levels of IL-2, IL-4, and IL-10, increases skin GSH, SOD, CAT, and GSH-Px activity, and decreases skin MDA levels.</td>
<td>15</td>
</tr>
<tr>
<td>Radix Rehmanniae</td>
<td>NF3, which comprises of Astragali Radix and Rehmanniae Radix in the ratio of 2:1(w/w)</td>
<td>Human skin fibroblast cell line Hs27</td>
<td>Up-regulates TGF-β1, BMP-6 synthesis, expression of type I and III collagens, fibronectin, and TIMP-1 and down-regulates MMP-9 expression in skin fibroblast cells. Regulates gene transcription for extracellular matrix synthesis via the Smad pathway and gene transcription for cell motility via the Ras/MAPK (non-Smad) pathway.</td>
<td>16</td>
</tr>
<tr>
<td>Radix Rehmanniae</td>
<td>2,5-Dihydroxyacetophenone (DHAP)</td>
<td>Mouse macrophages (RAW264.7)</td>
<td>Inhibits iNOS expression and NO production. Decreases levels of TNF-α and IL-6. Inhibits the phosphorylation of ERK1/2 and NF-κBp65.</td>
<td>17</td>
</tr>
<tr>
<td>Radix Glycyrrhizae</td>
<td>Extract</td>
<td>Mouse macrophages (RAW264.7)</td>
<td>Inhibits NO, TNF-α, IFN-γ, and IL-10 production.</td>
<td>18</td>
</tr>
<tr>
<td>Radix Glycyrrhizae</td>
<td>Liquiritigenin</td>
<td>Raw264.7 cells; rats (carrageenan-induced paw oedema)</td>
<td>Inhibits NF-κB DNA binding activity and iNOS expression. Suppresses the production of TNF-α, IL-1β, and IL-6. Inhibits the formation of paw edema induced by carrageenan.</td>
<td>19</td>
</tr>
<tr>
<td>Radix Glycyrrhizae</td>
<td>Radix Glycyrrhizae polysaccharide</td>
<td>Mice</td>
<td>Down-regulates the population of Treg cells and Foxp3 expression in Treg cells. Decreases IL-10 and TGF-β levels and increases IL-2 and IL-12p70 levels in serum.</td>
<td>20</td>
</tr>
<tr>
<td>Radix Astragali</td>
<td>Aqueous extract</td>
<td>BALB/c mice</td>
<td>Reduces the production of IgG2a and IgM and suppresses IL-6 production in spleen cells.</td>
<td>21</td>
</tr>
<tr>
<td>Radix Astragali</td>
<td>Aqueous extract</td>
<td>Zymosan air-pouch mice; Raw 264.7 cells</td>
<td>Reduces the expression of iNOS, COX-2, IL-6, IL-1β, and TNF-α. Decreases the production of NO. Attenuates the activity of p38 and Erk1/2 and stimulates MKP-1. Interferes with the translocation of NF-κB to the nucleus, subsequently results in NF-κB-dependent transcriptional repression.</td>
<td>22</td>
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<tr>
<td>Poria Cocos</td>
<td>PCP (an immunomodulatory protein purified from the dried sclerotium of Poria cocos)</td>
<td>RAW 264.7 macrophages cells</td>
<td>A potential immune stimulator. Induces TNF-α and IL-1β. Regulates NF-κB-related gene expression. Activates peritoneal cavity macrophages to induce Toll-like receptor 4 (TLR4)-mediated myeloid differentiation factor 88 (MyD88)-dependent signaling.</td>
<td>23</td>
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</table>
SLE with their mechanism of action on immunologic functions. Many physicians are aware of the potential for better treatment of SLE by combining TCM and Western medicine. This approach to the treatment of SLE can lead to an enhanced synergistic effect and also draw on unique advantages of each form of medicine, such as preventing infection, stabilizing a patient’s condition, reducing recurrence, and greatly improving the quality of life in patients with SLE. Over the past few years, TCM has made progress in treating SLE. Typically, Chinese herbal compounds are often combined with Western medicines such as corticosteroids and immunosuppressive agents in the integrative treatment of SLE in China. Several studies have examined such integrative treatment of SLE in patients. Combining the Lang-Chuang Medicinal Decoction with prednisone to treat SLE resulted in an efficacy of 93.33% (56/60) compared to 80% in the control group (40/50) (4). A double-blind, placebo-controlled study found that Ziyin Lupus Capsules combined with hormones were superior to hormones alone (5). Combining the Qingyang Toujie Mixture with prednisone tablets effectively improved the balance of Th1/Th2 cytokines and alleviated toxic and adverse reactions to hormone or immune inhibitors (6). Combining Qubanyangyin granules with conventional (Western) treatment improved clinical efficacy, reduced the toxic effects of conventional treatment, and decreased the rate of recurrence (7). Results of a double-blind, randomized controlled trial of the Dan-Chi-Liu-Wei combination (DCLWC) and conventional therapy to taper the steroid dose and prevent disease flare-ups suggested that combining DCLWC with conventional therapy to treat SLE was safe and may have a marginal effect on decreasing disease activity (8). Tapering of the steroid dose was not possible during the 6-month duration of the trial, and a long-term follow-up and large-scale studies are needed to confirm the effects of DCLWC.

**4. Conclusion**

TCM has gained increasing acceptance worldwide. Herbal medicines are generally low in cost, plentiful, and cause very little toxicity or few adverse reactions in clinical practice. Despite the vast interest and ever-increasing demand, the absence of strong evidence-based research and the lack of standardization of herbal products are the main obstacles toward the global adoption of TCM. A prescription for Chinese medicine may have multiple active ingredients delivering a comprehensive, integrated treatment of SLE via multiple targets and their associated pathways. If treatments are effective, then there must be underlying mechanisms that can be investigated and verified scientifically. Understanding these mechanisms can help to increase the efficacy of Chinese medicines in a logical and rational manner. Therefore, prospective randomized studies (or randomized controlled trials) in patients with SLE are needed to substantiate the use of TCM and an evidentiary basis for TCM also needs to be established as well.
References


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