DOI: 10.1089/act.2008.14105

Lupus Erythematosus and Herbal Medicine

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Abstract

Numerous herbal medicines show promise for helping people with systemic lupus erythematosus as well as discoid lupus. Herbs that can both suppress and enhance various aspects of the immune system, known as immunomodulators, are particularly interesting in these settings. *Trametes versicolor* (cloud mushroom, yun zhi), *Cordyceps sinensis* (cordyceps, duong chong xiao cao), *Ganoderma lucidum* (reishi, ling zhi), *Centella asiatica* (gotu kola), and *Urtica dioica* (nettles) have all been investigated as immunomodulators in relation to lupus. *Tripterygium wilfordii* (lei gong teng, thundergod vine) is the best-studied of the herbs that suppress the immune system and thereby relieve symptoms of lupus. *Artemisia annua* and *Artemisia apiacea* (sweet Annie, qing hao) are also being studied in this regard, as is *Nelumbo nucifera* (lotus). Additionally, phytoestrogens such as coumestrol may be valuable in treating lupus, though D-canavanine-containing seeds or sprouts of *Medicago sativa* (alfalfa) should be avoided. *Linum usitatissimum* (flax) seeds, as well as immunomodulators and thundergod vine, have all shown promise in patients with lupus nephritis.

Introduction

Mainstream treatments for discoid (DLE) or systemic lupus erythematosus (SLE) remain inadequate in terms of safety, efficacy, and cost effectiveness. This paper reviews herbal approaches that hold promise for improving this situation.

Immunomodulators

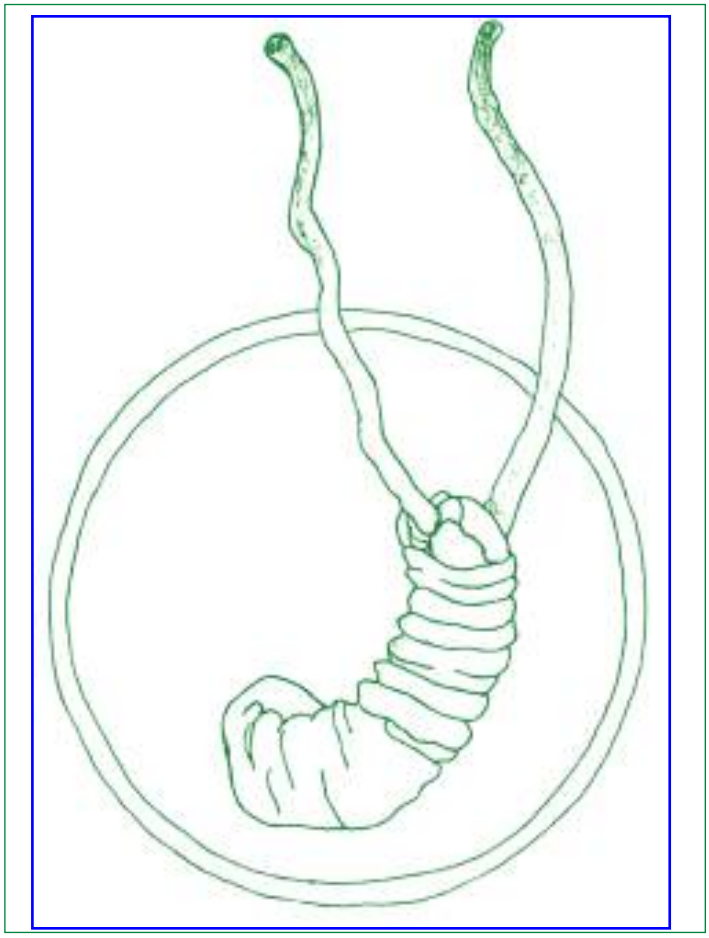
Immune dysfunction, particularly dysfunction in the complex regulatory network that links the immune and neuroendocrine systems, plays a central role in SLE. In traditional herbal medicine, herbs with immunomodulating properties have long been used for people with autoimmune diseases. These herbs generally have minimal or no known adverse effects and excellent cost-to-benefit ratio.

A glycoprotein extract dubbed PSK and derived from *Trametes versicolor* (cloud mushroom, yun zhi), formerly named *Coriolus versicolor*, has been shown to improve symptoms in patients with SLE.[1] This medicinal mushroom has long been valued in traditional Asian medical systems for syndromes that in the West are called cancers and autoimmune diseases. No other studies of PSK were reported after the promising preliminary trial described above. Large-scale trials of PSK and related extracts in patients with cancer show the extracts are very safe.[2] The usual dose in these trials has been 1–3 g daily.

Cordyceps sinensis (cordyceps, duong chong xiao cao) is a fungus that in the wild grows exclusively on a very specific caterpillar species and has a remarkably complex life cycle. This herb has been used in Traditional Chinese Medicine (TCM) for treating syndromes that in the West are considered autoimmune diseases. Preliminary studies in patients with SLE in China found that among other herbs, cordyceps could improve abnormal production of the immunoregulatory cytokine interleukin-2 (IL-2).[3] A follow-up trial found that a decoction of cordyceps prolonged the lifespan of female NZB/NZW F1 mice, a common animal model of SLE, and decreased anti-double–stranded DNA (anti-dsDNA) autoantibody production as compared to that in untreated controls. A steroidal saponin isolated from cordyceps and known as H1-A, when given orally for 8 weeks to male and female MRL 1pr/1pr mice, another animal model of SLE,[4] prolonged their lives and reduced the severity of proteinuria and lymphadenopathy, mesangial proliferation in the kidneys, and anti-dsDNA autoantibody production as compared to vehicle-treated controls. These results were confirmed in another study done with a crude aqueous extract of cordyceps in MRL 1pr/1pr mice.[5] These trials appear to strongly warrant trials of the effects of cordyceps extracts in human SLE patients.

Similar animal studies have been conducted using extracts of *Ganoderma lucidum* (reishi, ling zhi) mushroom or the closely related species *G. tsugae*. Extracts of *G. tsugae* were shown to reduce anti-dsDNA autoantibody formation, proteinuria, and cellular infiltration of internal organs and to prolong the lifespan of NZB/NZW F1 mice as compared to controls treated with prednisolone.[6]

No human trials have been reported of the use of reishi in SLE; however, an open clinical trial conducted in Germany of a standardized extract of triterpenoid glycosides of *Centella asiatica* (gotu kola) herb in doses of 60–120 mg per day in patients with SLE[7]



***Cordyceps sinensis* (cordyceps).**

found that the extract could produce symptomatic improvement. Gotu kola is considered an immunomodulating herb and is extremely safe.

A different approach was taken with a lectin isolated from *Urtica dioica* (stinging nettle) that eliminates the specific T-cell subset known as V beta 8.3+ cells and was shown to prevent development of any clinical signs of lupus or kidney damage when given to MRL lpr/lpr mice.[8] Although this information may be important in understanding the immune pathology of lupus, it also suggests that ingestion of certain herbs may be able to prevent onset of the disease in humans who are genetically susceptible or at risk for it. Whether stinging nettle would be useful in patients with established SLE is unknown, although this herb is traditionally used to reduce inflammation in such settings.

Immunosuppressants

Tripterygium wilfordii (lei gong teng, thundergod vine) is a native Asian plant whose roots have been determined to contain immunosuppressive glycosides. Only extracts of roots from which the bark has been removed should be used, in order to avoid amenorrhea, male infertility, kidney damage and leukopenia.[9] These effects are believed to be mediated by nontherapeutic alkaloids especially present in the bark, and whose concentrations may be further decreased by decoction. Another potential problem with long-term use of *Tripterygium* is decreased bone mineral density, although this is not as severe as that seen in women who take prednisone.[10] Any patient treated with *T. wilfordii* should have a monthly assessment of serum creatinine, complete blood count (CBC), and reproductive health.

All indications are that *T. wilfordii* works by immunosuppression and that the herb is not immunomodulating, in that it does not also work through immune activation.[11] The plant also has substantial activity involved in reducing inflammation.

Several clinical trials have been conducted on various extracts of *T. wilfordii* in patients with autoimmune disease. In an open trial, tablets providing 5 g of the whole root and stem, given three times per day to 15 patients with SLE and 8 patients with discoid lupus, were compared to prednisone given to 19 patients.[12] The two treatment agents were in general equally effective, although *T. wilfordii* eased arthralgia and rash significantly more effectively than did prednisone. Some kidney damage and leukopenia were seen in patients treated with *T. wilfordii*. Another open trial followed SLE patients treated daily with 30–45 g daily of decorticated stems and roots of *T. wilfordii*.[13] Symptoms were reduced and titers of antinuclear antibodies (ANA) and LE cell counts were improved. These laboratory results suggest the autoimmune process itself was inhibited. Occasional reversible amenorrhea and gastrointestinal upset occurred, which in most cases disappeared after a few days despite continued therapy.

A more recent trial looked at the effect of methylprednisolone (MP) followed by prednisone and *T. wilfordii* on 7 children with juvenile onset SLE without kidney or neurologic involvement.[14] Comparison groups were treated either with MP and cyclophosphamide (if they had nephritis or central nervous system [CNS] involvement, n = 18) or prednisone alone if they had no renal or CNS involvement (n = 5). Patients in the prednisone-only group fared far worse clinically (with 4 of these patients dying) than did those in the other two groups, which were otherwise fairly comparable to one another, particularly after 9 or more months of therapy. Two patients in each of the MP-plus-cyclophosphamide and *T. wilfordii* groups were asymptomatic 12 months after discontinuation of treatment. Frequent infections were not encountered in any of the study groups.

Animal studies have shown that the antimalaria agent artemisinin and its congeners, found in the plants *Artemisia annua* and *Artemisia apiacea* (sweet Annie, qing hao) have immunosuppressive properties.[15] Some preclinical research suggests these agents may actually be immunomodulatory.[16] While not all studies agree, this immunomodulatory capacity, coupled with the traditional use of these herbs for inflammatory conditions, supports the clinical potential of sweet Annie for treating SLE. Indeed, one preliminary trial in China found that *A. apiacea* was helpful in treating lupus, though full details of this study are not available in English.[17] Artemisinin at 200–600 mg daily was used successfully in another Chinese study, involving 25 patients with SLE.[18] *A. annua* was apparently also helpful in an open study of patients with DLE.[19]

Studies have shown that S-armepavine, an alkaloid isolated from *Nelumbo nucifera* (lotus) rhizome, inhibited T-lymphocyte proliferation in a mouse model of SLE.[20] Extracts of lotus rhizome, especially alcoholic extracts, have been shown to have strong antioxidant activity, which could help counteract some of the pathology of SLE.[21] Lotus rhizome is used primarily as an anti-hemorrhagic agent in TCM. Clearly, more research is warranted to determine the complete spectrum of action and utility of this intriguing herb in treating lupus.

Phytoestrogens

Estrogen and/or its metabolites have long been thought to play a role in SLE, largely because of the disease's preponderant occurrence in women. This, and evidence that environmental endocrine disruptors (xenoestrogens) can induce SLE-like syndromes in mice,[22] suggest that phytoestrogens may play a useful role in patients with SLE.

A study of the phytoestrogen coumestrol found that its administration was associated with decreased autoantibody production, reduced splenomegaly, and less severe proteinuria in NZB/NZW F1 mice.[23] Survival time did not differ from that of control groups not given coumestrol. This preliminary evidence supports the need for studies of other phytoestrogens and different dose levels of these substances, and human trials of phytoestrogens to see whether they will indeed be helpful. Studies of other phytoestrogens for lupus nephritis make this research even more important.

A phytoestrogenic herb that should be avoided in SLE is *Medicago sativa* (alfalfa). Sprouted forms of this herb contain the arginine homologue canavanine. This substance has been shown, in limited research, to potentially trigger SLE.[24] Although this is not apparently a common phenomenon, avoidance of canavanine by people with SLE is simply accomplished by avoiding any form of alfalfa that contains the seed.[25]

Lupus Nephritis

Glomerulonephritis is a common and serious complication of SLE, and as in the case of the other, botanical medicine also has much potential to help patients who develop lupus nephritis. One botanical that may have this capacity is *Linum usitatissimum* (flax) seed, which contains phytoestrogenic lignans and inflammation modulating omega-3 essential fatty acids. A single-blind, randomized clinical trial that gave 30 g per day of flax seeds for 1 year to 26 patients with SLE who were being treated with prednisone, followed by crossover to a year without the supplement,[26] unfortunately had many dropouts and poor follow-through, with only 9 patients clearly having taken the flax seeds as requested. Despite even this, there were clear indications that the 9 patients who did take the flax seed regularly experienced improvements in renal function.

Immunomodulators may also benefit patients with lupus nephritis. A 5-year open trial of lupus nephritis patients in China[27] compared the effects of a combination of cordyceps (1 g three times daily) and artemisinin (200 mg three times daily)—designated the immunomodulator group—with a combination of *T. wilfordii* and the multicomponent formula baoshenkang in 61 patients who had previously shown no response to corticosteroids or cyclophosphamide. Kidney function was stable in the immunomodulator group but declined in the control group. Clinically, patients in the immunomodulator group were rated significantly improved as compared to those in the control group. Adverse effects were also reportedly fewer in the immunomodulator group.

Conclusion

Numerous herbal medicines show great promise for mitigating SLE and lupus nephritis. Though much more research is needed in this area, strong preliminary indications are that various immunomodulatory, immunosuppressive, and inflammation-modulating botanicals may be of great benefit for these patients. □

References

1. Morimasa K, Yamana S, Matsueda H, et al. Immunostimulant therapy with protein-bound polysaccharide preparation (PSK) in patients with either SLE or RA. Clin Immunol 1980;12:393–398.

2. Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment [review]. Alt Med Rev 2000;5:4–27.

3. Chen JR, Yen JH, Lin CC, et al. The effects of Chinese herbs on improving survival and inhibiting anti-ds DNA antibody production in lupus mice. Am J Chin Med 1993;21(3–4):257–262.

4. Yang LY, Chen A, Kuo YC, Lin CY. Efficacy of a pure compound H1-A extracted from *Cordyceps sinensis* on autoimmune disease of MRL lpr/lpr mice. J Lab Clin Med 1999;134:492–500.

5. Fu T, Lin J. Effect of *Cordyceps sinensis* on inhibiting systemic lupus erythematosus in MRL 1pr/1pr mice [in Chinese]. Zhong Yao Cai 2001;24:658–659.

6. Lai NS, Lin RH, Lai RS, et al. Prevention of autoantibody formation and prolonged survival in New Zealand Black/New Zealand White F1 mice with an ancient Chinese herb, *Ganoderma tsugae*. Lupus 2001;10:461–465.

7. Wolram VS. Experiences with Maddecassol for the treatment of systemic lupus erythematosus [in German]. Wien Med Wschr 1965;115:439–442.

8. Musette P, Galelli A, Chabre H, et al. *Urtica dioica* agglutinin, a Vbeta8.3-specific superantigen, prevents the development of the systemic lupus erythematosus–like pathology of MRL lpr/lpr mice. Eur J Immunol 1996;26:1707–1711.

9. Werbach M, Murray M. Botanical Influences on Illness. Tarzana CA: Third Lines Press, 1994.

10. Huang L, Feng S, Wang H. Decreased bone mineral density in female patients with systemic lupus erythematosus after long-term administration of *Tripterygium wilfordii* Hook F. Chin Med J (Engl) 2000;113:159–161.

11. Tao X, Lipsky PE. The Chinese anti-inflammatory and immunosuppressive herbal remedy *Tripterygium wilfordii* Hook F. Rheum Dis Clin North Am 2000;26:29–50, [review: viii].

12. Wang BX, Yuan ZZ. A tablet of *Tripterygium wilfordii* in treating lupus erythematosus [in Chinese]. Zhong Xi Yi Jie He Za Zhi 1989;9:389,407–408.

13. Anonymous. *Tripterygium wilfordii* Hook F in systemic lupus erythematosus: Report of 103 cases. Chin Med J 1981;94:827–834.

14. Hu J, Li CW, Zhang X, et al. Methylprednisolone and cyclophosphamide pulse therapy of severe systemic lupus erythematosus in children [in Chinese]. Zhonghua Er Ke Za Zhi 2003;41:430–434.

15. Tawfik AF, Bishop SJ, Ayalp A, el-Feraly FS. Effects of artemisinin, dihydroartemisinin and arteether on immune responses of normal mice. Int J Immunopharmacol 1990;12:385–389.

16. Yang SX, Xie SS, Gao HL, Long ZZ. Artemisinin and its derivatives enhance T lymphocyte-mediated immune responses in normal mice and accelerate immunoreconstitution of mice with syngeneic bone marrow transplantation. Clin Immunol Immunopathol 1993;69:143–148.

17. Zhuang GK. Clinical study on the treatment of lupus erythematosus with *Artemisia apiacea* Hce [in Chinese]. Chung Hua I Hsueh Tsa Chih (Chinese Med J) 1982;62:365–367.

18. Zhong JX, et al. 25 cases of systemic lupus erythematosus treated by integrated Traditional Chinese Medicine and Western medicine. Chin J Integr Med 1999;19:47–48.
19. Zhao WF, Zhuang GK. Scanning electron microscopic evaluation of the treatment of discoid lupus erythematosus with qinghao. J Clin Dermatol 1987;16:126.
20. Liu CP, Tsai WJ, Shen CC, et al. Inhibition of (S)-armepavine from *Nelumbo nucifera* on autoimmune disease of MRL/MpJ-lpr/lpr mice. Eur J Pharmacol 2006;531(1–3):270–279.
21. Yang D, Wang Q, Ke L, et al. Antioxidant activities of various extracts of lotus (*Nelumbo nuficera* Gaertn) rhizome. Asia Pac J Clin Nutr 2007;16(suppl1):158–163.
22. Yurino H, Ishikawa S, Sato T, et al. Endocrine disruptors (environmental estrogens) enhance autoantibody production by B1 cells. Toxicol Sci 2004;81:139–147.
23. Schoenroth LJ, Hart DA, Pollard KM, Fritzler MJ. The effect of the phytoestrogen coumestrol on the NZB/W F1 murine model of systemic lupus. J Autoimmunity 2004:23;323–332.
24. Akaogi J, Barker T, Kuroda Y, et al. Role of non-protein amino acid D-canavanine in autoimmunity. Autoimmun Rev 2006;5:429–435.
25. Rosenthal GA, Nkomo P. The natural abundance of D-canavanine, an active anticancer agent, in alfalfa, *Medicago sativa* (L.). Pharm Biol 2000;38:1–6.
26. Clark WF, Kortas C, Heidenheim AP, et al. Flaxseed in lupus nephritis: A two-year nonplacebo-controlled crossover study. J Am Coll Nutr 2001;20(2suppl):143–148.
27. Lu L. Study on the effect of *Cordyceps sinensis* and artemisinin in preventing recurrence of lupus nephritis [in Chinese]. Xhongguo Zhong Xi Yi Jie He Za Zhi 2002;22:169–171.

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