Commentary

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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

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Table 1. Examples of compounds or extracts derived from traditional Chinese medicine being used to treat SLE

Main TCM herbs	Active component	*In vitro* and/or *in vivo* system	Target molecules and pathways	*Ref.*
Moutan Cortex	Paeonol	Rat	Reduces levels of TNF-α, IL-1β, and IL-6.	*9*
Moutan Cortex	Extracts	Human basophils (KU812 cells)	Suppresses the expression of ICAM-1 and the release of CCL2, CCL5, CXCL8, and IL-6.	*10*
Moutan Cortex	Extract containing paeonol and paeoniflorin	Human gingival fibroblasts	Inhibits activation of various inflammation-related genes.	*11*
Moutan Cortex	Extracts	Mouse model of type II collagen-induced arthritis (CIA)	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.	*12*
Moutan Cortex	Spray-dried moutan cortex extract	Mouse peritoneal macrophage	Inhibits the expression of iNOS and TNF-α release. Blocks the activation of NF-κB.	*13*
Radix Rehmanniae	Extracts	NC/Nga mice	Reduces the total number of mast cells, CCR3(+) eosinophil immunoreaction, and total serum levels of IgE, IL-2, and IL-4.	*14*
Radix Rehmanniae	Rehmanniae polysaccharides	Ultraviolet B (UVB) ray treated mice	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.	*15*
Radix Rehmanniae	NF3, which comprises of Astragali Radix and Rehmanniae Radix in the ratio of 2:1(w/w)	Human skin fibroblast cell line Hs27	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.	*16*
Radix Rehmanniae	2,5-Dihydroxyacetophenone (DHAP)	Mouse macrophages (RAW264.7)	Inhibits iNOS expression and NO production. Decreases levels of TNF-α and IL-6. Inhibits the phosphorylation of ERK1/2 and NF-κBp65.	*17*
Radix Glycyrrhizae	Extract	Mouse macrophages (RAW264.7)	Inhibits NO, TNF-α, IFN-γ, and IL-10 production.	*18*
Radix Glycyrrhizae	Liquiritigenin	Raw264.7 cells; rats (carrageenan-induced paw oedema)	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.	*19*
Radix Glycyrrhizae	Radix Glycyrrhizae polysaccharide	Mice	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.	*20*
Radix Astragali	Aqueous extract	BALB/c mice	Reduces the production of IgG2a and IgM and suppresses IL-6 production in spleen cells.	*21*
Radix Astragali	Aqueous extract	Zymosan air-pouch mice; Raw 264.7 cells	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.	*22*
Poria Cocos	PCP (an immunomodulatory protein purified from the dried sclerotium of *Poria cocos*)	RAW 264.7 macrophages cells	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.	*23*

Table 1. continued

Main TCM herbs	Active component	*In vitro* and/or *in vivo* system	Target molecules and pathways	*Ref.*
Chinese Yam	Diosgenin	BALB/c mice	Enhances OVA-specific serum IgG2a. Increases IFN-γ secretion and mRNA expression.	*24*
Fructus Corni	Aqueous extract	RAW 264.7 macrophage cells; mice	Inhibits the expression of COX-2 and iNOS and suppresses PGE2 synthesis and NO production. Down-regulates NF-κB. Suppresses the acetic acid-induced writhing response in mice.	*25*
Fructus Corni	7-*O*-galloyl-D-sedoheptulose	Type 2 diabetic db/db mice	Modulates protein expression of NF-κBp 65, COX-2, iNOS, JNK, phospho-JNK, AP-1, TGF-β1, and fibronectin.	*26*
Artemisia Annua	Ethanol extract	Mice	Suppresses splenocyte proliferation and reduces serum IgG, IgG1, and IgG2b antibody levels.	*27*
Artemisia Annua	Artemisinin	Lupus nephritis (LN) mice	Increases the expression of GRα mRNA and transcriptional coactivator P300 300/CBP protein	*28*
Artemisia Annua	Artemisinin	RAW264.7 macrophage cells	Induces the production of IL-12p40 by inhibiting JNK activity.	*29*

Abbreviations: AP-1, activating protein-1; BMP-6, bone morphogenetic protein-6; CAT, catalase; GSH-Px, glutathione peroxidase; CC, CXC, CCL, CXCL: chemokine; CCR, chemokine receptor; COX-2, cyclooxygenase-2; GR, glucocorticoid receptor; GSH, glutathione; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; iNOS, inducible nitric oxide synthase; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MDA, malonaldehyde; MKP-1, MAP kinase phosphatase-1; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; TNF, tumor necrosis factor; IL, interleukin; NO, nitric oxide; SOD, superoxide dismutase; TIMP-1, tissue inhibitor of metalloproteinases-1; TGF-β, transforming growth factor-β.

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

1. Han Y, Zeng F, Tan G, Yang C, Tang H, Luo Y, Feng J, Xiong H, Guo Q. Hydrogen sulfide inhibits abnormal proliferation of lymphocytes *via* AKT/GSK3β signal pathway in systemic lupus erythematosus patients. Cellular Physiol Biochem. 2013; 31: 95-804.
2. Bernknopf A, Rowley K, Bailey T. A review of systemic lupus erythematosus and current treatment options. Formulary. 2011; 46:178-182,191-194.
3. Zhang JL, Gong ZK. Relationship between the type of systemic lupus erythematosus according to Chinese medicine and expression of IL-10, IL-18, and Fas mRNA in peripheral blood mononuclear cells. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2009; 29:783-786 (in Chinese).
4. Liu SZ, Liu GX, Liu SY. Curative effect of integrative medical therapy for systematic lupus erythematosus. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2008; 28:994-997 (in Chinese).
5. Fan R, Wang Y, Wu XW. Evaluation of ziyin lupus capsules to treat inner heat due to a yin deficiency in systemic lupus erythematosus. Chin J Dermato Venerol Integ Trad W Med. 2006; 5:136-139 (in Chinese).
6. Huang GH, Chen YH, Duan HY, Liu Y, Linag XF, He YP, Wen XM, Xu QY, Zeng ZL, Zhong JX. Effects of qingyang toujie mixture in combination with prednisone tablet on Th1/Th2 cytokines in patients suffering from systemic lupus erythematosus. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2013; 33:172-176 (in Chinese).
7. Zhang J, Gao J, Xie J, Qiu X, Zhong L, He W. The effects of Qubanyangyin granules on decreasing toxicity and increasing efficacy during the treatment of patients with systemic lupus erythematosus. Rheumatism and Arthritis. 2012; 1:27-30 (in Chinese).
8. Liao YN, Liu CS, Tsai TR, Hung YC, Chang SJ, Lin HL, Chen YC, Lai HM, Yu SF, Chen CJ. Preliminary study of a traditional Chinese medicine formula in systemic lupus erythematosus patients to taper steroid dose and prevent disease flare-up. Kaohsiung J Med Sci. 2011; 27:251-257.
9. Fu PK, Wu CL, Tsai TH, Hsieh CL. Anti-inflammatory and anticoagulative effects of paeonol on LPS-induced acute lung injury in rats. Evid Based Complement Alternat Med. 2012; 2012:837513.
10. Liu KYP, Hu S, Chan BCL, Wat ECL, Lau CBS, Hon KL, Fung KP, Leung PC, Hui PCL, Lam CWK, Wong CK. Anti-inflammatory and anti-allergic activities of Pentaherb formula, Moutan Cortex (Danpi) and gallic acid. Molecules. 2013; 18:2483-2500.
11. Yun CS, Choi YG, Jeong MY, Lee JH, Lim S. Moutan Cortex Radicis inhibits inflammatory changes of gene expression in lipopolysaccharide-stimulated gingival fibroblasts. J Nat Med. 2013; 67:576-589.
12. Kim HS, Kim AR, Lee JM, Kim SN, Choi JH, Kim DK, Kim JH, Kim B, Her E, Yang YM, Kim HS, Kim YM, Choi WS. A mixture of Trachelospermi caulis and Moutan cortex radicis extracts suppresses collagen-induced arthritis in mice by inhibiting NF-κB and AP-1. J Pharm Pharmacol. 2012; 64:420-429.
13. Chung HS, Kang M, Cho C, Parvez S, Park CH, Kim D, Oh J, Kim H, Shin M, Hong M, Kim Y, Bae H. Inhibition of nitric oxide and tumor necrosis factor-alpha by moutan cortex in activated mouse peritoneal macrophages. Bio Pharm Bull. 2007; 30:912-916.
14. Kim MC, Lee CH, Yook TH. Effects of anti-inflammatory and Rehmanniae Radix pharmacopuncture on atopic dermatitis in NC/Nga mice. J Acupuncture and Meridian Studies. 2013; 6:98-109.
15. Sui Z, Li L, Liu B, Gu T, Zhao Z, Liu C, Shi C, Yang R. Optimum conditions for Radix Rehmanniae polysaccharides by RSM and its antioxidant and immunity activity in UVB mice. Carbohydrate Polymers. 2013; 92:283-288.
16. Zhang Q, Fong CC, Yu WK, Chen Y, Wei F, Koon CM, Lau KM, Leung PC, Lau CBS, Fung KP, Yang M. Herbal formula Astragali Radix and Rehmanniae Radix exerted wound healing effect on human skin fibroblast cell line Hs27 *via* the activation of transformation growth factor (TGF-β) pathway and promoting extracellular matrix (ECM) deposition. Phytomedicine. 2012; 20:9-16.
17. Han Y, Jung HW, Lee JY, Kim JS, Kang SS, Kim YS, Park YK. 2,5-Dihydroxyacetophenone isolated from Rehmanniae Radix Preparata inhibits inflammatory responses in lipopolysaccharide-stimulated RAW264.7 macrophages. J Med Food. 2012; 15:505-510.
18. Yue GGL, Chan BCL, Kwok H-F, To M-H, Hon KL, Fung KP, Lau CBS, Leung PC. Screening for anti-inflammatory and bronchorelaxant activities of 12 commonly used Chinese herbal medicines. Phytother Res. 2012; 26:915-925.
19. Kim YW, Zhao RJ, Park SJ, Lee JR, Cho IJ, Yang CH, Kim SG, Kim SC. Anti-inflammatory effects of liquiritigenin as a consequence of the inhibition of NF-κB-dependent iNOS and proinflammatory cytokines production. Br J Pharmacol. 2008; 154:165-173.
20. He X, Li X, Liu B, Xu L, Zhao H, Lu A. Down-regulation of Treg cells and up-regulation of TH1/TH2 cytokine ratio were induced by polysaccharide from Radix Glycyrrhizae in H22 hepatocarcinoma bearing mice. Molecules. 2011; 16:8343-8352.
21. Song Q, Kobayashi T, Xiu LM, Hong T, Cyong JC. Effects of Astragali root and Hedysari root on the murine B and T cell differentiation. J Ethnopharmacol. 2000; 73:111-119.
22. Ryu M, Kim EH, Chun M, Kang S, Shim B, Yu YB, Jeong G, Lee JS. Astragali Radix elicits anti-inflammation *via* activation of MKP-1, concomitant with attenuation of p38 and Erk. J Ethnopharmacol. 2008; 115:184-193.
23. Chang HH, Yeh CH, Sheu F. A novel immunomodulatory protein from Poria Cocos induces Toll-like receptor 4-dependent activation within mouse peritoneal macrophages. J Agric Food Chem. 2009; 57:6129-6139.
24. Jan TR, Wey SP, Kuan CC, Liao MH, Wu HY. Diosgenin, a steroidal sapogenin, enhances antigen-specific IgG2a and interferon-γ expression in ovalbumin-sensitized BALB/c mice. Planta Med. 2007; 73:421-426.
25. Sung YH, Chang HK, Kim SE, Kim YM, Seo JH, Shin MC, Shin MS, Yi JW, Shin DH, Kim H, Kim CJ. Anti-inflammatory and analgesic effects of the aqueous extract of corni fructus in murine RAW 264.7 macrophage cells. J Med Food. 2009; 12:788-795.
26. Park CH, Tanaka T, Yokozawa T. Anti-diabetic action of 7-*O*-galloyl-D-sedoheptulose, a polyphenol from Corni Fructus, through ameliorating inflammation and inflammation-related oxidative stress in the pancreas of type 2 diabetics. Biol Pharm Bull. 2013; 36:723-732.
27. Zhang YX, Sun HX. Immunosuppressive effect of ethanol extract of *Artemisia annua* on specific antibody and cellular responses of mice against ovalbumin. Immunopharmacol Immunotoxicol. 2009; 31:625-630.
28. Wu XL, Zhang WG, Shi XM, An P, Sun WS, Qiao

CL, Wang Z. Effect of artemisinin combined with glucocorticoid on the expressions of glucocorticoid receptor alpha mRNA, glucocorticoid receptor beta mRNA and P300/CBP protein in lupus nephritis mice. Chin J Integr Med. 2011; 17:277-282.
29. Cho YC, Lee SH, Lee M, Kim HJ, Oak MH, Lee IS, Kang BY. Enhanced IL-12p40 production in LPS-stimulated macrophages by inhibiting JNK activation by artemisinin. Arch Pharm Res. 2012; 35:1961-1968.

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