

Focus on Chinese herbal medicine therapy for multiple sclerosis by dialectical treatment

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Multiple sclerosis (MS) is a central nervous system (CNS) autoimmune disease that occurs in middle age, and it causes significant social and economic problems. The treatment effects of current modern western medicine on MS have increased. However, there are some serious side effects, such as progressive multifocal leukoencephalopathy and serious infections, which can result from universal immunosuppression.^[1-3]

To reduce the side effects of hormones and immunosuppressants, better results are required. Complementary and alternative medicines (CAMs) have been widely used to treat MS,^[4] and Chinese herbal medicine (CHM) is one of the main forms of CAM.^[5] To address the dilemma of the current situation with CHM, which is based on dialectical treatment, provides a new possibility to treat MS. There are many prescriptions for CHM that effectively treat MS/experimental autoimmune encephalomyelitis (EAE), but there is little information about the use of CHM for MS patients. Thus, it is important to understand CHM theory, especially for dialectic treatment of MS patients.

The pathogenic region of MS is believed to be located in the *brain medulla*. The *kidney* controls the congenital constitution, so dizziness, and depression are caused by insufficiency of the *kidney* essence and *marrow sea* insufficiency syndrome. On the basis of an ancient traditional Chinese medicine (TCM) textbook “Miraculous Pivot”, people who are in good health have sufficient *brain medulla*. Otherwise, patients will have vertigo tinnitus, tiredness, and weakness because of a lack of *marrow sea*. In modern TCM, some investigators support that *congenital deficiency syndrome* is a key factor in MS, and they show that most of the patients with MS have an empty *governor channel* and damage to the *kidney yang* and *brain marrow*.

The *spleen* and *stomach* support the acquired constitution and the source of *blood* and *vital energy*. Eye vision is based on blood nourishment and bad vision results from *spleen*, *stomach*, and *blood* deficiency. *Spleen* nourishes the muscles and limbs, and muscular atrophy occurs because of *spleen vital energy* deficiency.

The *liver* controls body liquid drainage. Depression is caused by hepatic *vital energy* that is stuck, dysphoria is caused by *liver vital energy* hyperfunction, and dementia is caused by both *liver vital energy* that is stuck and hyperfunction. The *liver* stores blood and controls vessels. Arthralgia is caused by *liver* dysfunction. Eye vision is also based on nourishment of the *liver* and *blood*.

Lung is the upper source of water, which is scorched by heat. *Spleen* controls skin and fur. Abnormal feeling and itching is caused by skin and fur that cannot be nourished by *body fluids*.

The *heart* stores the spirit and controls the mind. Devitalization of *heart yang* leads to mental fatigue. All itching and pain are caused by a heart disorder. *Heart* opens at the tongue. A soft and flexible tongue and fluent speech area result of *heart* blood that nourishes the tongue. However, dysarthria is caused by a lack of *heart* blood. In the ancient TCM textbook *Suwen*, it is suggested that the *heart* controls vessels and that vessels need warm *heart yang*.

Eight extra channels regulate *vital energy* and the blood. This shows that signs of weakness, numbness, sensory abnormalities, tremors, and ataxia are caused by losing *eight extra channels* of nutrition.

Exogenous disease invades the human body and results in dysfunction of the *five viscera* (*heart*, *liver*, *spleen*, *lung*, and *kidney*). (1) *Damp heat* damages the *spleen* and causes

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vital energy and blood loss at their source so that the limbs, eyes, muscle, fur, and tongue lose their source of nourishment. (2) *Cold qi* injures *yang qi* and causes whole-body stagnation. (3) *Wind pathogen* attacks the human body, so the patient appears to have vertigo, tremor, ataxia, and other symptoms, which are consistent with the course of MS.

Retention of phlegm and *fluid* is a pathological product of water and liquid metabolism. *Phlegm retention* causes stagnation of the *channel* and *vital energy*, abnormal sensation, numbness of limbs, and hemiplegic. *Phlegm retention* is when *Phlegm* gets stuck in the spleen and affects its transportation function. *Phlegm retention* can also deceive and disturb the mind, or cause lassitude, delirium, or madness. *Phlegm retention* is a *yin pathogen* that injures *yang qi*, so that it causes MS, which is a long-term disease that is difficult to treat. *Gore* is a pathological product of blood stasis in the body. *Gore* can affect the movement of *vital energy* and blood and the formation of new blood, and cause choroid stasis and loss of nourishment.

Buyang Huanwu (BYHW) decoction has seven ingredients and is based on invigorating vital energy and activating blood circulation and collaterals as an auxiliary. The sovereign drug is *Astragalus mongholicus*, which promotes *vital energy* to activate the blood by increasing the dose. The minister drug is *Radix Paeoniae*, which cools and activates the blood. *Ligusticum wallichii* promotes vital energy to activate the blood, and Peach seed and Red flower speed blood circulation and remove blood stasis. *Angelica sinensis diels* supports blood and speeds blood circulation, while *Pberetima* clears and activates the channels and collaterals. All of them are adjunctive drugs. Investigators have repeatedly studied the effect of BYHW on immune regulation of EAE mice, and it is suggested that BYHW can reduce the neurological function score of EAE mice after treatment. It can also play a role in anti-inflammation and immunomodulation by inhibiting the Rho-associated coiled-coil forming kinase II/Toll-like receptor 4/nuclear factor- κ B inflammatory pathway and regulatory T cells.^[6,7]

Formerly known as *Erhuang Fang*, *Bushen Yisui* (BSYS) decoction consists of ten ingredients. *Radix rehmanniae recens* and prepared rehmannia root are monarch drugs; they nourish the kidney yin and brain marrow, which both play a role in helping and promoting vital energy. *Fritillaria thunbergiimiq* and *Gastrodiaelata* dissipate phlegm and soothe the wind, while leenurus and heterophyllus speed blood circulation and remove blood stasis; all of these are ministerial drugs. *Leech* and *Scorpio* dispel *pathogenic qi*. The whole prescription has the effect of tonifying the kidney, removing phlegm, and activating blood circulation, and has an obvious effect on MS patients with kidney deficiency and phlegm stasis obstruction. Studies showed that BSYS and its individual components could decrease the nerve function score in EAE mice at different times and to different degrees, and they also play a neuroprotective role in reducing infiltration in inflammatory cells, demyelination, and axonal injury. The results showed that BSYS can alleviate patients'

clinical symptoms in the acute phase of MS and significantly reduce recurrence in patients who insist on taking it during the remission period. Additionally, even if it recurs, the symptoms will be mild.^[8,9]

Erhuang fang could reduce CNS infection and demyelination in EAE, and it also worked in MS patients. This might be explained by *Erhuang Fang*, which inhibited interleukin (IL)-4 and Th1/Th2 in EAE. Furthermore, evidence for *Radix Rehmanniae* such as BSYS capsules, *Liuwei Dihuang* (LWDH) pills, *Zuogui* pills, and *Yougui* pills also supports the above ideas in MS/EAE.^[10-12]

Catalpol is an extraction from the root of *Rehmannia*, which has been shown to be neuroprotective in the CNS, especially for EAE. *Catalpol* was shown to have good effects on infiltration and demyelination, and *Catalpol* could reduce Th17 cell levels, increase chondroitin sulfate proteoglycan 4 (NG2/CSPG4) and myelin basic protein expression in mice brains, and increase *Olig1* and *Olig2* gene and protein expression.^[12]

LWDH, *Zuogui* pills, and *Yougui* pills have positive effects on neuroprotective and immunoregulation in MS/EAE. LWDH consists of six ingredients that nourish *yin*, support the kidneys, and feed the marrow. For EAE mice, LWDH could reduce the neurological score and inflammatory infiltrates. Furthermore, LWDH could reduce tumor necrosis factor alpha (TNF- α) protein and mRNA expression and the TNF- α /transforming growth factor beta (TGF- β) ratio, suggesting that it regulates the balance Th1/Treg cells.^[10-12]

Hyungbangpaedok San (HBPDS) is a classic TCM formula that is named *Jingfang Baidu San*. It is composed of ten ingredients.^[13] Choi *et al*^[13] reported that HBPDS showed good results on treating EAE mice. HBPDS reduced demyelination and infiltration on EAE, and reduced mRNA expression of pro-inflammatory cytokines and chemokines. HBPDS also inhibited changes in the blood-brain barrier such as astrocytes, adhesion molecules, and junctional molecules.

Yin-deficiency in the liver and kidney is treated by *Yiguan Jian* (YGJ). This formula consists of eight ingredients. *Radix rehmanniae recens* nourishes the blood to replenish the liver and kidney, and it is the monarch drug. *Adenophora stricta* and *Radix Ophiopogonis* nourish *yin* and generate water. *Angelica sinensis diels* nourishes the blood and promotes blood circulation, and *Fruit of Chinese wolfberry* nourishes the liver and kidney. *Radix Paeoniae Alba* nourishes hepatic *yin*. *Cynomorium songaricum* tonifies the kidney and nourishes the blood. A small amount of *Chinaberry fruit* relieves liver *qi*, so that the drugs commonly play a role in nourishing *yin* and soothing the liver. The effects of YGJ on the symptoms, inflammatory plaque, and serum IL-10, interferon- γ and TGF- α were shown in EAE rats, and the EAE onset time was delayed, clinical symptoms were alleviated, and Th1 cells were inhibited.

Wendan decoction is a classic prescription for *phlegm* and *beat* syndrome. The formula consists of eight ingredients.

Rhizoma Pinellinae Praeparata reduces stomach adverse effects and dries dampness and *phlegm*, and it is the monarch drug. *Bambusae caulis imtaeniam* clears away heat, resolves *phlegm*, stops vomiting, and removes annoyance. *Fructus aurantii immaturus* promotes *qi* and dissipates *phlegm* and makes *phlegm* follow *qi*; all of these are ministerial drugs. *Dried tangerine* or *orange peel* regulates the flow of vital energy and eliminates dampness. *Semen coicis* and *Poriacocos* invigorate the spleen and infiltrate dampness. All of these are adjuvar, and their total effect is on dampness, *phlegm*, *qi*, and the stomach.

Huangqi Guizhi Wuwu (HQGZWW) decoction is a common prescription for arthromyodynia. The formula consists of five ingredients. *Astragalus mongholicus* tonifies *qi* and replenishes the *wei-energy*. *Cassia twig* disperses wind and cold and warms Meridians through Arthralgia, and both of them are ministerial drugs. *Ginger* disperses wind evil, which can help *Cassia twig*. *Fructus Ziziphi Jujubae* nourishes the blood and replenishes *qi*, which can help *Astragalus mongholicus* and *Radix Paeoniae Rubra*. Huang *et al* treated EAE rats with HQGZWW decoction, and IL-35 expression in the TCM group was significantly higher compared with the control group, suggesting that HQGZWW could increase IL-35 levels in the peripheral blood of EAE rats. The immune response of Th1 and Th17 cells may be inhibited, which results in inhibition of the immune response and reduction of EAE severity.

All prescriptions and their ingredients are presented in Supplementary Table 1, <http://links.lww.com/CM9/A370>.

In summary, the etiology and pathogenesis of MS in TCM are complicated because TCM is the mixture of Chinese traditional philosophy and medicine. Dialectical classification is also different from benevolence and wisdom, and it is difficult to say which treatment is right. Moreover, dialectical treatment in TCM can improve the patients' symptoms, prolong the remission period, and control the recurrence period. To reduce hormone and immunosuppressant side effects, more ideal results are required. Faced with the current dilemma of western medicine treatment, TCM treatment which is based on dialectical treatment, provides a new possibility for treating MS. The etiology and pathogenesis of MS and its dialectical rules require further investigation, and determination of a unified dialectical standard, evaluation standard, and treatment plan. This review summarizes the clinical characteristics of TCM in MS treatment, and provides effective evidence for future use of TCM in MS.

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Conflicts of interest

None.

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