



Traditional Chinese Medicine in Multiple Sclerosis: Theory and Practice

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Abstract

Purpose of review Multiple sclerosis (MS) is a disease with complex etiology and pathophysiology. Approved drugs for MS treatment are only partly effective, and some of them show obvious side effects and resistance. In this review, we will discuss the philosophy and advantages of traditional Chinese medicine (TCM) as a complementary and alternative therapy for MS treatment. The purpose of this review is to provide novel insights and directions for MS management.

Recent Findings TCM is an empirical medical system which has established its own unique method of diagnosis and therapy for over thousands of years. The concept of holism and yin-yang balance are its core theories. From TCM perspective, syndrome differentiation, deficiency tonification, stasis removal, and detoxication are the four main principles of MS treatment. Clinical trials have shown that TCM is effective to alleviate symptoms, prevent recurrence, and delay disease progression in MS patients. Experimental evidences also have confirmed the effect of TCM in experimental autoimmune encephalomyelitis (EAE), which is in the multitarget and multicomponent pattern. TCM maximize therapeutic efficacy by facilitating synergistic actions, exhibiting various biological activities including anti-inflammatory, anti-oxidative, immune-regulatory, and neuro-protective effects in MS and EAE. Treatment with TCM alone or combined with western medicine can greatly improve the body's resistance and reduce side effects of the treatment.

Summary Integrating TCM with Western medicine have great promise for inspiring new ideas and therapies for prevention and treatment of MS. The appropriate combination can improve efficacy, reduce toxicity, and make the best benefits in MS patients.

Keywords Multiple sclerosis · Traditional Chinese medicine · Therapy · Holism · Yin-yang balance

Introduction

Multiple sclerosis (MS), one of the most common inflammatory demyelinating diseases in the central nervous system (CNS), is becoming the major cause of chronic disability, especially in young adults. Advances have been achieved in understanding the pathogenesis of MS in the past few years, yet exact mechanisms remain to be elucidated [1]. Currently approved drugs

for baseline therapy of MS, including glucocorticosteroid, interferon-beta, glatiramer acetate, teriflunomide, fingolimod, natalizumab, and mitoxantrone are only partly effective in halting disease activity and disability progression. And some of them show obvious side effects and resistance [2]. Therefore, more attention should be paid to exploring the complementary and alternative therapies for MS.

As an empirical medical system independent of Western medicine, traditional Chinese medicine (TCM) has established its own unique method of diagnosis and treatment for over thousands of years. TCM has become the most popular modality of complementary and alternative medicine (CAM) in chronic diseases, treatment resistance, and intolerance of synthetic modern drugs, either in China or abroad [3, 4]. In recent years, clinical practices have confirmed that TCM is effective to alleviate clinical symptoms, prevent recurrence, delay the disease progression, and improve quality of life (QOL) in MS patients [5–8]. Widely applied as part of the integrative therapy in China, TCM anticipate in all the aspects of MS including prevention, acute period, and remission [7, 8]. However, the intersection and consistency in the cognition

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of TCM and Western medical system in MS still need to be clarified. This review will summarize TCM in MS treatment from its own theory and relate mechanism annotation by modern western medicine.

The Essential Theory in TCM

Different from Western medicine reduction theory (scientific evidence for the diagnosis and treatment of a specific disease), TCM doctors understand disease from the concept of holism (a reflection of the integrity of the human body, the natural and the social environment) [9••, 10, 11]. It compares the physiological and pathological changes of the human body with the natural normal or abnormal status by analogy and classification and infers the internal essence according to external symptoms and signs [11, 12]. That is, TCM emphasizes the harmony of the human body itself and its related surrounding environment. Therapies of TCM are based on syndrome differentiation (a summarization of physiological function and pathological changes of the disease at different stages) [12–14]. In a TCM prescription, doctors should address the status of various organs and tissues in the human body and their relevant circumstance. They can treat different diseases with the same prescription or treat the same disease with different therapies (the treatment method changed mainly based on function status of related organs and tissues) [9••, 12]. Hence, there is always no quantitative diagnosis in TCM as that of Western medicine, which mainly focuses on the disease itself. The theory of yin-yang (positive and negative syndrome) is the principle of syndrome differentiation [9••, 12]. In TCM, the occurrence and development of diseases lie in the imbalance between yin and yang. Based on the concept of holism, TCM doctors developed different therapeutic methods (including herb medicine, acupuncture, Qigong, cupping glass, etc.) to balance excessiveness or deficiency of yin and yang, among which, herbs (natural medicine) is the most popular. They may neglect the building components of herbal medicine and their detailed mechanisms with drug targets (the prescriptions were harmonizing but the medicines were not) [12, 15]. To some degree, TCM is a mixture of Chinese philosophy, culture, ritual, and medical practices [15, 16].

The Pathogenesis of MS in TCM

In Yellow Emperor's Canon of Medicine (a classic of internal medicine written during the period 770–221 BC) [9••], the pathological locations of MS are encephala, spinal cord, and governor meridian (which run along the middle of the vertebra column till the head and get into the brain) [17]. They influence the viscera including heart, spleen, liver, lungs, kidneys, and various tissues (not the anatomical organs and tissues in

Western medicine) [18]. According to the holism theory, the interactions of these vital organs and tissues in the human body and other external factors such as daily rhythmicity, seasons change, and surrounding stress decide the occurrences, development, and remission of MS [7, 8, 9••].

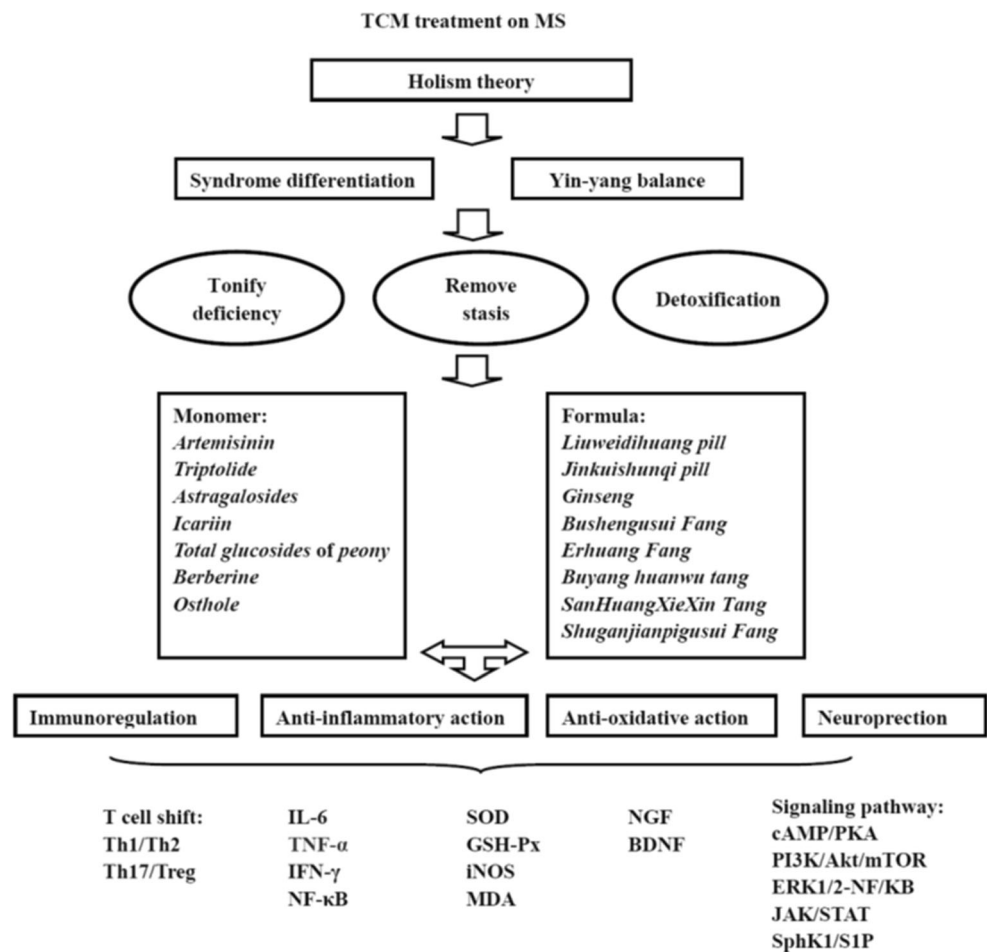
From syndrome differentiation perspective, MS is defined belonging to deficiency, stasis, and toxin syndrome [7, 8, 15]. Deficient syndrome is body resistance weakness. The clinical manifestation of deficiency syndrome in MS may be fatigue, heavy limbs, paralysis, and laziness [7, 8, 9••]. Deficient syndrome is closely associated with immune function in MS patients, and deficiency tonification (strengthening the body resistance) is a fundamental TCM therapy in MS [7, 8]. The stasis syndrome is caused by the obstruction of Qi (the vital substance that comprises the human body and maintains life activities and physiological functions of the viscera) and blood [19]. The most frequently cited stasis syndrome in MS patients exhibits with a dark purple tongue, face, and eye with purple black shadow, fixed pain, blurred vision, etc. [7, 8, 19]. Invigorating Qi and promoting blood circulation to remove stasis is always powerful in MS treatment. The toxin can impede and weaken the function of viscera and tissues, lead to senility and degeneration, which could manifest as pain and numbness, changing emotion and cognition, and make the diseases become lingering or chronic [7, 8]. Meanwhile, toxicity syndrome can be seen in the whole course of MS patients and detoxication method of TCM runs through in MS therapy [7, 8].

In essence, deficiency, stasis, and toxin syndrome in MS patients is the imbalance of yin-yang, the core theory of TCM. Thus, the balance of yin and yang from syndrome differentiation (deficiency tonification, remove stasis removal, and detoxication) is the principle treatment of MS patients. TCM doctors use individualized treatment plans for different MS patients (“tailored to the patients”) to improve different symptoms. The concept of holism is always appreciated as the ancient wisdom of herb medicine combination in MS patients. Although the complexity of the herbs combination used in MS patients is different from Western medicine, an increasing body of scientific data has begun to reveal their commonalities (Fig. 1).

Are Yin-Yang Balance Effects of TCM Consistent with Immunomodulatory Effects of Western Medicine in MS Patients?

From TCM perspective, the pathogenesis of MS is the imbalance of yin and yang, then the disharmony of internal pathophysiological functions and the external natural environment. Therefore, the treatment of MS is to regain a new dynamic balance of yin and yang through pattern identification to recuperate and avoid further damage [7, 8, 9••]. Yin-yang imbalance mechanism of MS defined by TCM has a similar pathological mechanism to that defined by Western medicine. MS is an autoimmune disease defined by Western medicine.

Fig. 1 Diagram shows Chinese holism theory and Western medicinal mechanisms of Traditional Chinese Medicine in multiple sclerosis



The abnormal shift of immune cells particularly Th1/Th2 or Th17/Treg cells is the fundamental immune dysfunction in MS patients. The management strategy is immune-regulatory therapy [1, 2]. The aberrant Th1/Th2 and Th17/Treg cell shift is imbalance between yin and yang in the view of TCM to some degree. Regaining yin-yang balance for MS treatment by TCM is similar to promote Th1/Th2 and Th17/Treg cell in expectant shift in Western medicine. Previous researches had found that Chinese herbal medicines or their extracts could balance yang and yin as well as keep Th1/Th2 and Th17/Treg normal shift in MS patients. Among them, *Liuweidihuang pill* and *Jinkuishenqi pill* are the typical prescriptions which have yin-yang balance effects in MS treatment [20–22]. Both of the formula contains *Radix Rehmanniae* and *Fructus Corni (preparata)* in *Liuweidihuang pill* but not in *Jinkuishenqi pill*, *Rhizoma Dioscoreae*, *Cortex Moutan*, *Rhizoma Alismatis*, etc. Although the formula seems similar, the differences of ingredients and processing methods produce different pharmacological effects. *Liuweidihuang pill* have clinical efficacy for treatment of yin deficiency syndrome while *Jinkuishenqi pill* is a classical Yang-reinforcing prescription [20, 21]. TCM doctors prescribe *Liuweidihuang pill* or *Jinkuishenqi pill*

alone or in combination according to the yin-yang theory. Modern pharmacological studies have shown that both *Liuweidihuang pill* and *Jinkuishenqi pill* could suppress experimental autoimmune encephalomyelitis (EAE, a well-established animal model of MS) by promoting Th17 to Treg cell shift via regulating the cytokines of tumor necrosis factor- α (TNF- α), TGF- β , and IL-17 [20, 21].

Ginseng (the root of *Panax ginseng*), one of the most well-known oriental medicinal herbs, has been widely used as a herbal remedy for various disorders such as MS. Ginseng contains various pharmacological components such as *ginsenosides*, *polyacetylenes*, *polyphenolic compounds*, and *acidic polysaccharides*. Ginseng itself has yin-yang balance effects in TCM. As an immune-enhancement agent, ginseng has been extensively reported to maintain homeostasis of the immune system in modern medicine [23]. It could improve the activity of natural killing cells, stimulate T cell proliferation, and promote the generation of Treg cells in EAE mice. Moreover, ginseng was reported to increase serum IL-4, reduce interferon-gamma (IFN- γ), IL-1 β , and IL-17, promote Th2 shift, and attenuate the severity of MS [23].

From the TCM perspective, herb itself or in combination with other herbs (as form of decoction, pills, capsules, tablet,

etc.) is the most popular prescription in MS patients. However, most of the mechanistic studies of their effects on MS have been done based on the active components which always worked as a monomer in modern science. *Artemisinin* is an active component of *Artemisia annua*. It is cold in character and acrid in taste, which belongs to yin from drug properties of TCM. *Artemisinin* could shift the immune responses from Th1 to Th2 and *promote* the proliferation of Treg cells, then decrease severity of EAE progression [24–27]. *Triptolide* is the most active ingredients in *Tripterygium wilfordii* Hook (a climbing shrub with a long history of diverse use in TCM). It has cold character and bitter taste, which belongs to yin in nature as *Artemisia annua*. Previous studies have demonstrated that triptolide could ameliorate EAE development by regulating Th1-, Th2-, and Th17-related cytokine, therefore regulating T cell proliferation and activation [28–33]. Yang in nature, *astragalosides* is the principle bioactive component extracted from the roots of *Radix Astragali*. It has a warm character and sweet taste and has been used widely as a key remedy in TCM for enhancing yang. It was found that astragalosides could attenuate severity of EAE and prevent inflammatory cell infiltration in spinal cords of EAE mice [34, 35]. The mechanism was decreased mRNA expression of transcriptional factors ROR γ t and up-regulation of Foxp3 to modulate Th17/Treg cell differentiation [34, 35]. Other monomers such as *baicalin* from *Scutellaria baicalensis* and *arctigenin* from *Arctium lappa* (both belongs to yin) have similar immunomodulatory effects, which are mainly summarized in Table 1 [36–39].

From above, we can see that the yin-yang balance treatment in MS/EAE by TCM is similar to the immunomodulatory effects in Western medicine to some degree. Apparently, the prescription underlying philosophical systems of TCM theory in MS patients is more complex than “one drug, one target, and one disease” approach in modern medicine [12]. And benefits of TCM treatment in MS patients cannot be disregarded due to inadequate international treatment standardization and quality control from the view of modern science [40].

Does the Function of Deficiency Tonification, Stasis Removal, and Detoxification of TCM Act as Anti-inflammatory, Anti-oxidative, and Neuroprotective Effects in MS Patients?

From syndrome differentiation, MS was defined belonging to deficiency, stasis, and toxin syndrome [5–8]. They can interact and transform with each other and decide the occurrence, progress, and remission of MS [7, 8]. The biomarkers of deficiency, stasis, and toxin syndrome detected by modern science are different combinations of IL-6, IL-1, TNF- α , IFN- γ , IL-4, IL-10, NF- κ B, SOD, GSH-Px, iNOS, MDA, NGF, etc. [5–8]. There are also biomarkers to detect the inflammatory,

oxidative stress, and neuroprotective effects of Western medicine in MS treatment.

Bushengusui Fang is a traditional Chinese formula used to tonify deficiency for MS patients. The ingredients are *Epimedium* Linn, *Radix Salviae miltiorrhizae*, *Rehmannia glutinosa*, *Radix Curcumae*, *Cistanche deserticola*, and other herbs. It could improve symptoms and signs of MS patients and reduce recurrent frequency (Table 2) [41, 42]. *Bushengusui Fang* could remarkably reduce incidence of EAE, inhibit inflammation and demyelination of brain and spinal cord, and reduce serum IL-6 and TNF- α in EAE mice [41, 42]. *Erhuang Fang* is a classical TCM formula that has the tonic effects in MS patients. It consists of *Radix Rehmanniae*, *Radix Rehmanniae Preparata*, *Leech* (the dried body of *Whitmania pigra*), *bulbus Fritillariae thunbergii*, *scorpion* (the dried body of *Buthus martensii*), and *Radix Polygoni Multiflori*. *Erhuang Fang* could relieve inflammatory reaction and demyelination in EAE rats, reducing the activities of NK cells and serum IL-6 level to attenuate EAE [43]. Moreover, *Erhuang Fang* could reduce the relapse rate and annual relapse rate in MS patients (Table 2) [44]. *Icariin* is a primary active component of *Epimedium extracts* (a tonic medicine of TCM), which has the anti-inflammation and neuroprotective effects in degeneration disease including MS. It is effective in ameliorating neurological signs of EAE via mediating estrogen receptor β , modulating HPA function and glucocorticoid receptor expression [45]. *Catalpol* is from *Radix Rehmanniae*, a tonic medicine of TCM. It could improve neurological function, reduce inflammatory cell infiltration and demyelination, and promote the expressions of Olig1 and Olig2 transcription factors in EAE mice [46]. Both the above-mentioned formulas and monomer can improve MS/EAE through tonifying deficiency from syndrome differentiation.

Buyang Huanwu Tang is a popular TCM formula to invigorate Qi and promote blood circulation then remove stasis in MS patients. The formula consists of *Radix Astragali*, *Radix Angelicae Sinensis*, *Radix Paeoniae Rubra*, *Rhizoma Chuanxiong*, *Flos Carthami*, *Semen Persicae*, and *Pheretima*. Recent studies showed that *Buyang Huanwu Tang* could provide anti-inflammation and neuroprotective effects in EAE mice. It could inhibit the inflammatory cell infiltration and demyelination in the spinal cord of EAE [47, 48]. It could also regulate the proportion of peripheral T cell subsets, promoted the conversion of M1 macrophages into M2 phenotype in the spinal cord and spleen, and inhibited ROCKII/TLR/NF- κ B signaling pathway [47, 48]. *Total glucosides of peony* (TGP) is an active compound extracted from the roots of *Paeonia lactiflora* Pall which can remove stasis in TCM. TGP has been used in the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [49, 50]. Additionally, pharmacological studies have shown the antiallergic, anti-inflammatory, anticancer,

Table 1 Summary of selected herb medicine for EAE and their biofunction

List	Herb medicine	Active ingredients	Modes of delivery	Biofunction	Ref.
1	<i>Artemisia annua</i> L.	Artemisinin, artesunate	Oral, intraperitoneal	Inhibit inflammatory mediators and migration of pathogenic T cells to the CNS, shift the immune responses from Th1 to Th2, and promote the expansion of regulatory T cells	[24–27]
2	<i>Tripterygium wilfordii</i> Hook. f.	Triptolide, celastrol	Intraperitoneal	Inhibit the mRNA expression of both Th1 and Th17 cytokines, down-regulate ERK1/2-NF- κ B and JAK/STAT signaling pathways, and reduce NF- κ B expression and nitrites levels	[28–33]
3	<i>Radix astragali</i>	Astragalosides	Oral	Decreased mRNA expression of ROR γ t but up-regulated that of Foxp3 to modulate Th17/Treg cell differentiation	[34, 35]
4	<i>Scutellaria baicalensis</i>	Baicalin	Intraperitoneal	Promote the apoptosis of inflammatory cells, prevent Th1 and Th17 cell differentiation via STAT/NF- κ B signaling pathways, and inhibit expression of proinflammatory molecules and chemokines	[36, 37]
5	<i>Arctium lappa</i>	Arctigenin	Intraperitoneal	Inhibit Th17 cell differentiation and proliferation, activate AMPK and inhibit phosphorylated p38, up-regulate PPAR- γ , and suppress ROR- γ t	[38, 39]
6	<i>Epimedium</i> extracts	Icarin	Oral, intraperitoneal	Ameliorating neurological signs of EAE via mediating estrogen receptor β , modulating HPA function and glucocorticoid receptor expression	[45]
7	<i>Radix Rehmanniae</i>	Catalpol	Oral	Improve neurological function, reduce inflammatory cell infiltration and demyelination, and promote the expressions of Olig1 and Olig2 transcription factors	[46]
8	<i>Paeonia lactiflora</i> Pall	Total glucosides of peony	Oral	Modulate the secretion of IFN- γ , IL-4, IL-10, and IL-17, regulate the expression of T-bet, ROR γ t, GATA3, and Foxp3, and prevent the reduction of BDNF and CNPase expression	[49–51, 52•]
9	<i>Berberis vulgaris</i>	Berberine	Oral	Reduce the permeability of BBB, suppress the increased expression of MMP-9, inhibit gelatinase activity, reduce laminin degradation, and inhibit the SphK1/SIP signaling pathway	[56–58]
10	<i>Cnidium monnieri</i> (L.) Cuss	Osthole	Intraperitoneal	Induce the expression of NGF and inhibit the expression of IFN- γ and anti-inflammatory capacity to neural stem cell-based therapy	[59, 60, 61•, 62]
11	<i>Achillea millefolium</i> L.	Luteolin, apigenin	Oral, intraperitoneal	Improve mature of oligodendrocyte precursor cells, delay the recovery of behavioral deficits, modulating dendritic cell and other immune cell functions	[63, 64]
12	<i>Sophora flavescens</i>	Matrine	Intraperitoneal	Promote regeneration of the injured CNS via increased cAMP/PKA expression, reduce BBB leakage, inhibit activities of MMP-2 and MMP-9, promote oligodendrocyte differentiation and myelination by activating the PI3K/Akt/mTOR signaling pathway, and reduce oligodendrocyte apoptosis via regulation of ProNGF and NGF signaling	[65–70]

Table 2 Summary of RCTs using herbal therapy for patients with multiple sclerosis

Herbal formulas	Patient number	Diagnostic criteria	Treatment group	Control group	Duration of treatment	Follow-up period	Safety	Positive result	Negative result	Ref.
Bushengusui tablet	36	McDonald	Herb tablet 6#tid + control therapy	MT 1000 mg/day for 3–5 days + prednisone 60–580 mg/day	3 months	Not stated	GSWT	Total clinical efficacy rate, EDSS, average length of stay	Non	[41, 42]
Erhuang formula	67	McDonald criteria	Herbs 1 dose/day + control therapy	MT 1000 mg/day gradually halved every 3 days to 120 mg/day + prednisone 60 mg/day	Not stated	2 years	GSWT	Relapse frequency	EDSS, annual relapse rate	[43]
Erhuang formula	65	Poser	Herbs 1 dose/day + control therapy	MT 1000 mg/day for 6 days + prednisone 60 mg/day	Not stated	1 year	GSWT	EDSS	Annual relapse frequency	[44]
Shuganjiampiguisui Fang	35	McDonald	Herbs 1 dose/day + control therapy	MT 1000 mg/day gradually halved every 3 days to 120 mg/day + prednisone 60 mg/day reduced weekly 10 mg/day	3 weeks	Not stated	GSWT	Annual relapse frequency and interval	Non	[83]
Shuganjiampiguisui Fang	70	McDonald	Herbs 1 dose/day + control therapy	MT + Danhong + citicoline + vitamin C + potassium chloride	2 weeks	Not stated	Gastro-intestinal reaction	Total clinical efficacy rate, EDSS	Non	[84]
Yiqihuoxuehuatan soup	42	Poser	Herbs 1 dose/day + control therapy	MT 1000 mg/day for 5 days + prednisone 40–60 mg/day	1 month	Not stated	GSWT	Total clinical efficacy rate, EDSS	Non	[85]
Buyang Huanwu decoction	65	Poser	Buyang Huanwu decoction + control therapy	MT 1000 mg/day for 5 days + prednisone 40–60 mg/day	4–6 weeks	Not stated	GSWT	Total clinical efficacy rate, EDSS	Non	[86]

GSWT, generally safe and well tolerated; MT, methylprednisolone; EDSS, Expanded Disability Status Scale

antioxidant, immunomodulatory, and neuroprotective properties of this medicinal herb [51]. In our recent study, TGP can effectively ameliorate EAE through reducing secretion of IFN- γ , upregulating of BDNF and CNPase expression [52]. From above, removing stasis can alleviate MS and EAE from syndrome differentiation in TCM.

SanHuangXieXin Tang (*Samhwangsasim-tang* in South Korea and *San'o-shashin-to* in Japanese) is a traditional herbal medicinal formula containing *coptidis rhizome*, *rhei rhizome*, and *scutellariae Radix* which has effects of detoxication from TCM. According to previous laboratory and clinical studies, *SanHuangXieXin Tang* has anti-inflammatory, anti-oxidative, and anti-apoptotic activities and plays an important role in the treatment of cardiac disorder, hepatic, and Parkinson's disease [53, 54]. It exerts a protective effect on EAE mice through reduction in BBB permeability, inhibiting recruitment of Th1 cells, increasing Tregs cells and significantly down-regulating expression of p-IkBa, NF-kB (p65), p-ERK, p-JNK, and p-P38 in the spinal cords in EAE mice [55]. *Berberine* is an *isoquinoline derivative alkaloid* isolated from *Berberis vulgaris* which has the function of detoxication. Our previous study showed that *berberine* could reduce the permeability of BBB, suppress the increased expression of MMP-9 [56] and provide a neuroprotective effect by inhibiting gelatinase activity and reducing laminin degradation [57]. Meanwhile, *berberine* has also been reported to suppress demyelination and loss of neurophysiological function by inhibiting the SphK1/S1P signaling pathway [58]. These findings further support that *berberine* can be a potential therapeutic agent for MS. *Osthole* is a bioactive coumarin derivative from *Cnidium monnieri Cuss*, which has detoxication effects in TCM and possesses a variety of pharmacological and biochemical properties of anti-inflammation action or immunomodulatory effects [59, 60]. *Osthole* was found to ameliorate clinical severity of EAE mice by inducing the expression of NGF and inhibiting the expression of IFN- γ both in the brain and sera of mice in vivo and in splenocytes in vitro [61]. Recently, *osthole* has been further reported to confer a potent anti-inflammatory capacity to neural stem cell-based therapy in EAE [62]. From above, detoxication can alleviate MS and EAE from syndrome differentiation. Other monomers such as *luteolin* and *apigenin* from *Achillea millefolium L*, *matrine* from *Sophora flavescens* has similar effects which are mainly summarized in Table 1 [63–70].

Syndrome differentiation which emphasizes individualized treatment is dynamic and flexible in MS therapy. TCM doctors practice different kinds of herb medicine and matched different MS patients with their own characteristics [7, 8, 14]. Undoubtedly, the therapy of syndrome differentiation has positive effectiveness in MS patients. Because the concept is difficult to be comprehend from a modern biomedical perspective which builds on evidence-based theoretical interpretations and solid evidence of syndrome-based effects,

syndrome differentiation is often avoided or underestimated, which reduces the potential benefits [14]. From above, we found that the concept of tonifying deficiency, removing stasis, and detoxication, which is the principle of TCM treatment, could work by their anti-inflammatory, anti-oxidative, and neuroprotective effects in MS patients.

Are Treatments for MS with Concept of Holism in TCM Consistent with Disease-Modifying Therapy in Western Medicine?

In the perspective of the holism theory of TCM, everything is interconnected and grasping the whole nature of MS is very important [9, 10]. Based on the pathogenesis, syndrome patterns, and different disease stages, TCM doctors prescribe various formulas for MS patients with different characters. The therapy goals are balancing yin-yang and harmonizing of internal function and external circumstances. The TCM doctors emphasize both “regulation” and “cure” to maintain stabilization of aberrant immune system in MS patients, to ameliorate symptoms and signs, minimize disability, and reduce relapse or progression [7, 8, 9, 10].

The prescription emphasizes the unity of herb or formulas (multiple herbs). The combination of several herbs exhibits various biological activities and is not the heap of medicines. In modern pharmacology, the mechanism of formula of TCM can be explained by the following hypothesis: TCMs render effects and weaken toxicities through the additive effects of numerous effective forms (including their constituents or/and metabolites) on the same target, the synergistic effects are based on the overall action of the additive effects on individual targets and their toxicities' scattering effects [12, 16, 71]. The advantages of multitarget including anti-inflammatory, immune-regulatory, anti-oxidative, and neuroprotective effects on MS, gradually improve patient's resistance and prevent possible adverse effects [5, 6]. For TCM, the formula should be evaluated as a whole and any separation will inevitably result in a decrease or even an offset in its performance.

The holism theory agrees with disease-modifying therapy (DMT) in MS patients at current time [5, 6]. DMT is defined as an intervention that alters the expected natural course of MS other than simply improve symptoms, thereby gradually improving patient's QOL [3, 5, 6, 72]. QOL is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a multidimensional concept related to physical, psychological, and social functioning and worked as an evaluation index for health and the curative effect of disease [72]. QOL evaluation system is consisted of the core theory of holism which emphasizes harmony of human body, the nature, and the society [72].

Treatment concept of MS which fuse TCM and Western medicine will pay more attention to analyzing the nature of each patient and produce more effective strategies.

Why Not Integrate the TCM and Western Medicine to Produce Better Effects on MS Patients?

TCM emphasizes the holistic nature of the body and the subjective experiences of patients and doctors [40, 73]. The effect of MS treatment always depends on the practitioners' own experiences and patient feedback, as well as the internal logic and systematic basis of Chinese medicine's philosophy. It is relatively flexible and versatile. And the therapeutic efficacy cannot be verified by single standardized intervention necessary in randomized clinical trials (RCTs) [74]. The difference between TCM and modern medicine is significant, and the TCM, which is under the guide of integral view, is in great "incommensurability" with the modern science and technology, which is under the guide of reduction theory [11, 12, 75, 76]. The modern methods are not always suitable for TCM research. As Prof. Xueseng Qian said, the theory of TCM is not natural science. It is natural philosophy which is based on phenomenological cognition and demands a comprehensive understanding which is not restricted to science [77].

Fortunately, the development of technology provides a new possibility to the modern transformation of TCM study [78–80]. Techniques including biospecific cell extraction, serum pharmacology, and TCM network pharmacology are widely used for screening and analysis of TCM prescriptions [81]. Other researches on syndrome element differentiation based on phenomenology and mathematical method are also used to integrate TCM and Western medicine [76]. At present, a lot of work has been done to recognize and separate the active components in herbal medicines effective for MS. And many classic formulas have been modified by modern techniques and applied in clinical practice. The mechanism about these single agents and modified formulas has been implied. However, it must be noticed that the compounds in herbal medicines often modulate and modify the effects of the active ingredient in the herbs, so an extracted active ingredient from the herb alone may not ensure the therapeutic effect in clinic.

Even so, integrating TCM with modern medicine have great promise for inspiring new ideas and therapies for preventing and treating MS [4–6], a disease which has complex etiology and pathophysiology without specificity and effective treatment. Appropriate combination of Eastern and Western concepts may have positive effects. Recent research has shown that *Icariin* has synergistic effects with methylprednisolone to ameliorate EAE. The combination of *Icariin* and methylprednisolone could modulate HPA functions, promoting anti-inflammatory and anti-apoptotic effects via

decreasing serum IL-17 and CORT concentrations, up-regulating the expression of GR in cerebral white matter and attenuating the cell apoptosis in spinal cord [82]. Other clinical practice such as *Shuganjianpigusui Fang* (mainly consisted of *Bupleurum chinense*, *Paeonia lactiflora* Pall, *Angelica sinensis*, *Atractylodes macrocephala*, *rhizoma smilacis glabrae*, *Glycyrrhiza uralensis* Fisch), *Yiqihuoxuehuatan soup*, or *Buyang Huanwu Tang* can be combined with methylprednisolone in MS patients is in practice. The combination significantly reduced the annual relapse in the treatment group (Table 2) [83–86]. The appropriate combination cannot only improve treatment efficacy but also reduce drug dosages and adverse reactions in MS patients [87].

Conclusions

In conclusion, although TCM and Western medicine have evolved on distinct philosophical foundations and reasoning methods, an increasing body of scientific data has begun to reveal their commonalities. This review provides a new insight in intergradations of the TCM and western medicine in MS management, and appropriate combination is promising. Because herbal medicines have diversified ingredients and probably cause interactions when combined with chemical medicines, attention should be paid to mutual metabolism interference between herbals and drugs then to avoid potential side effects.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no financial or other conflicts of interest.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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