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The “Treatise on the spleen and stomach” (*Pí Wèi Lùn*) as the first record of multiple sclerosis in the medical literature – A hypothesis based on the analysis of clinical presentation and herbal medicine

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ABSTRACT

Background: The “Treatise on the spleen and stomach” (*Pí Wèi Lùn*) is the work of the scholar and physician *Li Gao* (Jin-Yuan dynasties, 1115–1368 C.E., China). *Li Gao* described a clinical presentation that today would fall under the diagnosis of Multiple Sclerosis (MS) and proposed the treatment with herbal medicine and nutritional guidelines. The *PWL* is well known for its application in the treatment of MS and autoimmune conditions. However, this theoretical “MS” has not yet been analyzed through a scientific investigation, and research on its herbal formulations for MS is scant.

Methods: We analyzed the *PWL* “MS” clinical presentation considering biomedical diagnostic criteria and neurological correlates. To support our review, we searched Pubmed for studies on the *PWL* main herbal formulas and their herbs/isolates used for the believed “MS” which treated experimental autoimmune encephalomyelitis (EAE)/MS.

Results: We found a very close correlation between the *PWL* “MS” and the current MS diagnosis. Twenty four studies on the herbs-isolates showed significant amelioration of EAE, neuronal damage, and demyelination.

Discussion: Collectively, *Astragali radix*, *Ginseng radix*, *Glycyrrhizae radix*, and *berberine* containing *Phellodendri cortex* reduced the severity of EAE through different signaling pathways and mechanisms of action. These herbs provided a wide range of properties such as anti-inflammatory, anti-oxidant, anti-microglial activation, anti-infiltration of leukocytes, apoptotic/anti-apoptotic balance, and neuronal protection.

Conclusion: Our review proposes that the *PWL* is the first record of MS in the medical literature. Its formulas and herbs-isolates offer a fertile area for MS research and an invaluable potential for its treatment.

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1. Historical background

The earliest well-documented case in the Western world of a condition which today falls under the diagnosis of Multiple Sclerosis (MS) is dated back to the 14th century, Holland.¹ St. Lidwina of

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Schiedam (1380–1433 C.E.), who was canonized by Pope Leo XIII (1890), suffered from a mysterious symptomatology after a skating accident in 1396 (Table 1). In 1979, Medaer compared Lidwina’s reported clinical history to the Schumacher diagnostic criteria. He concluded that “MS existed in the 14th century”¹, which established it as the first evidence of possible MS in the medical literature.

Jean Cruveilhier and Sir Robert Carswell are credited with the first clinical descriptions of MS.¹ However, there is some controversy on whose work took precedence. Cruveilhier and Carswell worked independently, but their illustrations of the MS lesions appeared publicly almost simultaneously.² Cruveilhier’s work was

Abbreviations

APG	Acidic Polysaccharide of Panax ginseng
APS	Astragalus Polysaccharides
ASI-IV	Astragaloside IV
AST	Astragalus
BBB	Blood-brain barrier
BBR	Berberine
BDNF	Brain-Derived Neurotrophic Factor
CAM	Complementary and Alternative Medicine
CAMs	Cell Adhesion Molecules
CAT	Catalase
DMTs	Disease-modifying therapies
EAE	Experimental Autoimmune Encephalomyelitis
ECM	Extracellular Matrix
FOXP3	Forkhead box P3
GA	Glycyrrhizic Acid
GL	Glycyrrhizin
GR	Glycyrrhizae radix
GRA/GA	18-β-glycyrrhetic acid
GRx	Glutathione Reductase

GSH	Glutathione
HMGB-1	High-mobility Group Box 1
HQGP	Huang Qi Glycoprotein
KRGE	Korean Red Ginseng
LicoA	Licochalcone A
MAP-2	Microtubule Related Protein-2
MBP	Myelin Basic Protein
MMP	Matrix Metalloproteinase
MOG	Myelin Oligodendrocyte Glycoprotein
NGF	Nerve Growth Factor
Neu-N	Neuron Nuclear Antigen
NMO	Neuromyelitis Optica
OLG	Oligodendrocyte
OPC	Oligodendrocyte Precursor Cell
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
S1P	Sphingosine 1-Phosphate
SphK1	Sphingosine Kinase 1
TBARS	Thiobarbituric Acid Reactive Substances
TCM	Traditional Chinese Medicine.

composed of two volumes with the title dates from 1835 to 1842, and with the MS lesions appearing in the 1835 volume. Carswell's atlas was published in 1838³. Some historians credit Cruveilhier with the first illustrations of the MS lesions.³ For others, the entire Cruveilhier's work was only published in 1842 which then would place it after Carswell's publication.² Regardless, MS was only delineated in 1868 when the French physician Jean-Martin Charcot provided a detailed description of the MS lesions (*“la sclérose en plaques”*). He correlated the postmortem findings with clinical symptoms and described the different forms of MS.⁴ The research done by Charcot cemented our present biomedical knowledge of MS.

Another study that should be mentioned is the article by Holmøy (2006).⁵ He talks about the accounts of Bishop Thorlak, the *“Elder Book of Portents”*. In this book, there is a description of a woman named Halldora who got very sick and was cured through the believed healing powers of Bishop Thorlak. Thorlak who died in 1193 was later canonized. Halldora presented with walking and sitting difficulties, almost no strength of limbs, pain, and short periods of improvement. She was bedridden for three years and had to be carried everywhere. The author then added that the symptoms were possibly exaggerated to dramatize the curing

powers of Bishop Thorlak, and that the disease could correspond to the relapsing-remitting form of MS (RRMS), chronic inflammatory demyelinating polyneuropathy or muscular transmission disease.⁵ Holmøy's conclusion is about the presence of temporary paralysis in medieval Europe, and the author provides no proof to defend Halldora's case as being MS.⁵ Therefore, we were unable to acknowledge this account as a possible case of MS due to lack of evidence. The *“Elder Book of Portents”* seems to be, according to what is portrayed, more about Bishop Thorlak's divine accomplishments than a report and exploration of causes and treatment of diseases.⁵

In China, the first official documented case of MS was registered in the *Xiehe* hospital in 1926, and the first MS autopsy report was done in the *Huashan* hospital in 1957.⁶ The work of the scholar and physician *Li Gao*, aka *Li Dong Yuan* (1180–1251 C.E.) of the *Jin-Yuan* dynasties (1115–1368 C.E.) is considered of special importance for the study of MS in Traditional Chinese Medicine (TCM).⁷ In his masterpiece, the *Pi Wei Lun* (*PWL* 脾胃论 “Treatise on Spleen and Stomach”), *Li Gao* described a clinical presentation that today would possibly fall under the diagnosis of MS.⁷ The *PWL* is well known by scholars and physicians for the application of its knowledge in the treatment of MS and other autoimmune conditions.⁷ However, its historical importance and placement in the medical literature regarding MS have not yet been investigated through scientific analysis, and research on its herbal formulations for MS is scant. The present research is the first historical review on the *PWL* and on its reported description of a disease compatible with MS. Two *PWL* herbal formulas are especially considered for the treatment of “MS”, *Huáng Qí Rén Shēn Tāng* (*HQRST* 黄芪人参汤 “Astragalus and Ginseng Decoction”) and *Bú Zhōng Yì Qì Tāng* (*BZYQT* 补中益气汤 “Tonify the Middle and Augment the Qi Decoction”). *HQRST* can be considered a modification of *BZYQT*, and it is the specific formulation indicated for the theoretical “MS” described in the *PWL*⁷ (Fig. 1).

We investigated whether the *PWL* can be considered the first documentation of MS in the medical literature, and the existing evidence on the use and efficacy of its herbal formulas for experimental autoimmune encephalomyelitis (EAE)/MS. EAE is the murine model of MS used for research purposes.

Table 1

St. Lidwina of Schiedam's clinical presentation analyzed by Medaer (1979) which led to the recognition of the first record of MS in the medical literature.

First record of MS in the medical literature (Medaer, 1979)
Walking difficulties
Violent lancinating pain (trigeminal neuralgia?)
Headaches
Body pain
Split face and hanging lip (facial paralysis?)
Blindness of right eye
Sensitivity of left eye
Paralysis of both legs
Paresis of right arm
Sensibility disturbances
Wounds (decubitus ulcers?)
Dysphagia
Flank pain (acute renal block?)

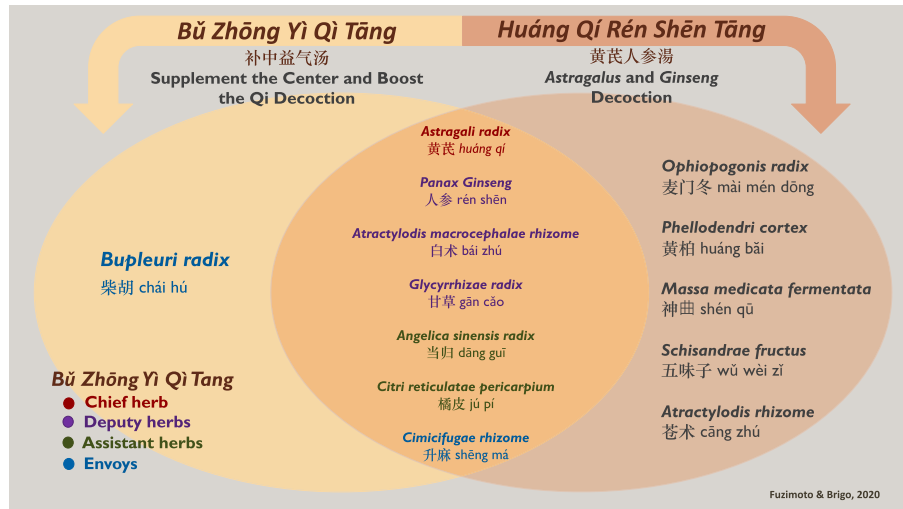


Fig. 1. The hierarchical structure of TCM herbal formulas. *Bǔ Zhōng Yì Qì Tāng* (BZYQT 补中益气汤 “Supplement the center and boost the Qi decoction”) is composed by the chief, the deputy, the assistant and the envoy herbs to address the therapeutic principle of “tonifying the middle burner and raising the Yang”. The herbal formula *Huáng Qí Rén Shēn Tāng* (HQRST 黄芪人参汤 “Astragalus and Ginseng decoction”), can be considered a modification of *Bǔ Zhōng Yì Qì Tāng*, and the seven herbs that overlap both formulas are displayed in the intersection of the circles. In *Huáng Qí Rén Shēn Tāng*, the use of *Atractylodis rhizome* (苍术 *cāng zhú*) is recommended instead of *White Atractylodis* (白朮 *bái zhú*) when there is no sweating (Shou-Zhong & Jian-Yong, 1993).

1.1. The increasing demand for TCM treatment modalities for MS

In 2013, it was estimated that 2.3 million people suffered from MS worldwide.⁸ The pharmacotherapies used for MS have the objective of slowing disease course, treat relapses and manage symptoms. However, some immune-modulators and immune-suppressant agents can cause serious adverse effects and challenge treatment adherence.⁹ Some patients do not have a positive response to disease-modifying therapies (DMTs), and others are even refractory to all such drugs.⁹ Most MS patients will utilize DMTs at one point during their illness, but many people will temporarily or permanently quit the treatment.⁹ Recently, a systematic review to assess the benefits and harms of the long-term use of DMTs was prepared for the Agency for Healthcare Research and Quality at the U.S. Department of Health and Human Services. In their report, the researchers discovered that “there was insufficient evidence for long-term benefits for DMTs for secondary progressive MS patients, and most outcomes for relapse-remitting MS patients”.¹⁰ In the United States, the cost of DMTs for MS went from the annual average of US\$8,000–10,000 in 2004 to US\$60,000 in 2015.¹¹ The annual cost for self-administered MS DMTs quadrupled from 2006 to 2016 representing a 12.8% increase per year.¹² In 2017, the report done by the Institute for Clinical and Economic Review (ICER) showed the annual costs of sixteen MS DMTs. The wholesale acquisition cost (WAC) went for example, from US\$33,408 for Rituximab, to US\$72,359 for Interferon β -1b, and up to US\$103,749 for Alemtuzumab.¹³ In another example, the Pharmacoeconomic Review Report (2017) revealed that the cost of a 10 mg tablet of Cladribine as US\$ 3,082.70 making an annual average of US\$43,158 for a person weighting 70 kg.¹⁴ The extreme high cost of the DMTs and the lack of compliance to medications are some of the factors that contribute to the patients looking for Complementary and Alternative Medicines (CAMs).⁹ CAMs are prevalent in 33%–80% in the MS patients.¹⁵ In the U.S., 19.9% of 3,140 MS patients used Acupuncture, 26.6% used herbs and the more dissatisfied people were with conventional medicine the more likely they were to use CAMs.¹⁶ The use of CAMs for MS has somewhat been documented but there is not much in-depth research on what TCM can offer for MS, especially regarding herbal medicine.¹⁷ The continuing

development of autoimmune conditions and the increasing use of alternative treatments represent a great demand for TCM research for MS.

2. Approach

We used the translation of the *PWL* in English published by Blue Poppy Press.⁷ This translation was based on the *Yi Tong Zheng Mai*, considered a well-preserved and the most reliable version from the Ming dynasty published by the People’s Health & Hygiene Press in 1957.⁷ We thoroughly examined the “MS” *PWL* clinical presentation to find modern neurological correlates matching the terminology used. To support our overview, we searched Pubmed for articles in English that investigated the two main *PWL* herbal formulas applied as treatment for the theoretical MS, *BZYQT* and *HQRST*. In addition, we used the same search parameters to look for primary data in controlled clinical trials that investigated all the single herbs that compose the two formulas and specifically examined their effects and mechanisms of action on EAE/MS. The terms (“multiple sclerosis” OR “experimental autoimmune encephalomyelitis” OR EAE) were accompanied by “AND” followed by the herbal keywords: “bu zhong yi qi tang”, “huang qi ren shen tang”, ginseng, (glycyrrhizae OR glycyrrhiza), (astragalus OR astragali), (atractylodis OR atractylodes), (“angelica sinensis” OR “angelicae sinensis”), (“citri reticulatae” OR “citrus reticulata”), (cimicifuga OR cimicifugae), (bupleuri OR bupleurum), (ophiopogonis OR ophiopogon), (phellodendri OR phellodendron), “massa medicata fermentata”, (schisandrae OR schisandra), and berberine. We also examined the bibliographical references of each article found and looked for any additional research that we might have missed in the primary search.

3. Discussion

3.1. The “MS” clinical presentation in the *PWL*

In the translation of the *PWL*, chapter 3/book 2 (page 85) is entitled “Diseases in the different seasons due to spleen and stomach vacuity weakness and formula composing according to different

diseases”.⁷ Here we transcribed the narrative of the theoretical MS in its entirety as it appears:

“When the spleen and stomach are vacuous and weak, the qi of the upper burner is insufficient. In summer, the original qi is damaged by intense heat, (giving rise to) fatigue, somnolence, debilitated limbs, insufficient essence spirit, atonic flaccidity of the legs, cold inversion in the mornings and evenings, and fire-like heat coming back with the yang qi becoming effulgent when the sun is hanging high. Since both yin and yang, qi and blood are insufficient, there occur heat inversion with yin vacuity or cold inversion with qi vacuity (with) inability to taste food, fire sparks emitted in the eyes, blurred vision, frequent urination, difficult voiding of bound stools, ventral pain in the cardiac region, flank pain or acute spasm, tightening below the umbilicus as if bound by ropes or, in the extreme, stabbing (lower abdominal) pain, difficulty relaxing the abdomen, obstruction in the chest, frequent retching or dry retching or coughing with phlegm, foaming at the mouth, rigidity of the tongue, pain in the upper and lower backs, scapulae, and eyes, frequent headache, inability to take in food or (too easily) feeling satiated on eating, no desire to eat, particularly severe spontaneous sweating, and (feeling of) yin qi shrouding the skin and hair (referred by the author as chills or feeling of cold). It is hot weather that exacerbates the disease. All this is brought by geng, the large intestine and xin, lung metal, which are overwhelmed by heat. (In this case), one must first assist the original qi and regulate the insufficient geng and xin. (For this), Huang Qi Ren Shen (Tang) (Astragalus & Ginseng Decoction) is indicated”.

3.1.1. Analysis of the PWL “MS” clinical presentation

Here we discuss the evidence regarding the possible “MS” diagnosis in the PWL. We analyzed the reported clinical presentation in light of the latest scientific research and diagnostic criteria. This condition cannot go through an evaluation according to any MS diagnostic criteria such as the Schumacher, Poser or the McDonald criteria due to the evidence of lesions only in space but not in time. The lesions in space refer to the central nervous system (CNS) involvement of different sites which leads to the manifestation of signs and symptoms. The lesions in time denote the appearance of lesions over a period, which is impossible to know here. This imposes considerable limitations for our analysis. It is also impossible to characterize the MS phenotype for the same reason. Nonetheless, upon a neurological evaluation, we believe that this is very likely MS.

Some symptoms are especially indicative of MS. The presence of “fire-like heat being caused and worsened during summer time” can be interpreted as the Uhthoff’s phenomenon (UP). In the UP, studies show a decrease in conduction velocity of demyelinated axons in response to an increase in body temperature causing temporary worsening of neurological symptoms.¹⁸ The UP is typically encountered in MS but appears in other demyelinating conditions such as Neuro Myelitis Optica (NMO).¹⁹ Until recently, NMO was considered a subtype of MS due to a similar clinical presentation. However, in 2004 upon the publication on the association between NMO and an antibody against aquaporin 4 (anti-AQP4 Ab) or NMO-IgG, NMO started being considered a different disease.²⁰ Demyelinating NMO is generally more violent and devastating than MS.²¹ In more than 85% of the NMO patients, attacks happen in the form of optic neuritis (ON), transverse myelitis (TM) or both.²¹ In 50% of the cases, it results in paralysis or blindness within 5 years.²¹ Often, NMO patients with TM of the cervical spine develop respiratory failure and death. NMO can be especially destructive if no treatment is applied. ON in MS is generally temporary and reversible. Thus, we hypothesized that the PWL pattern resembles more the

manifestations of MS than of NMO.

We tried to establish the correspondence between the symptoms of the PWL and their Western medicine equivalents (Table 2). Some of the terminologies are unique to the TCM’s jargon. Thus, interpretation was carried out assisted by existing published scientific data and our clinical experience. Some symptoms, although not exclusive to MS, are very common in this disease. The blurry vision and “fire sparks emitted in the eyes” imply inflammation in the eyes. Optic neuritis (ON) is often the first manifestation of MS, and diplopia and nystagmus are also frequently found.^{22,23} ON may be present in 20% of the clinical isolated syndrome (CIS) cases, and it may develop in 50% of the MS patients during the course of disease.^{22,23} The central fatigue is caused by demyelination in the CNS and is reported in 80% of the MS cases.²⁴ We interpreted the “insufficient essence spirit” as depression or imbalanced emotional states which are widespread among MS patients. Depression is present in 50% of the cases, anxiety in 36%, and pseudobulbar affect (PBA) in 10%.²⁵ The “flank pain or acute spasm” was recognized as the “MS hug”. Pain is a problem encountered in at least 50% of MS patients²⁶, and headaches are common in 78% of the cases.^{27,28} Another series of manifestations may be attributed to a dysfunction of the autonomic nervous system (ANS) such as “cold inversion in the morning and evenings, spontaneous sweating, and feeling of Yin Qi shrouding the skin and hair”, the latter explained as “chills or a feeling of cold”.^{29,30} The “difficulty voiding of bound stools” was identified as constipation, common in 50% of the MS patients.³¹ A few symptoms not characteristic of MS also appear such as “obstruction of the chest, frequent retching, and coughing of phlegm”. These may be explained by stress or digestive problems which are frequent in MS patients. All symptoms and their correlations can be seen in Table 2.

Our assessment indicates that this is probably MS and that it may be the first documentation of MS in the medical literature. Before the present study, the first record of MS was manifested in the person of St. Lidwina of Schiedam (1380–1433 C.E.).¹ Expert physicians who examined her had no knowledge of the cause of her disease which was attributed to God’s divine intervention.¹ European medieval medicine was focused on religious beliefs rather than on a scientifically structured medicine.⁴¹ Conversely, by the Jin-Yuan dynasties in China, medicine had evolved into a systematically structured and complete medical system with its own diagnostic patterns, anatomic models, and physiopathological processes.⁴² This systematization classified diseases according to the understanding of all natural phenomena, and the physicians could prescribe organic and inorganic compounds seen as “drugs”.⁴² Li Gao’s participation in this systematization process was very important. The differences between the medicines in China and Europe’s Middle Ages were striking. A more sophisticated practice at that point reinforces the likelihood of a TCM diagnosis of a believed MS, and the remedies to address it as illustrated in the PWL.

3.2. The herbal formulas in the PWL as a remedy for the MS pattern

Right after the description of the theoretical PWL MS pattern on page 85, Li Gao continues immediately on page 86 by giving the herbal formula that would remedy such clinical manifestation, *Huang Qi Ren Shen Tang* (HQRST 黄芪人参汤 “Astragalus and Ginseng Decoction”).⁷ We transcribed below the components of this formula exactly as they appear in the PWL.

“Radix Astragali Seu Hedysari (Huang Qi), 1 qian; add 1 qian in case of excessive spontaneous sweating

Rhizoma Cimicifugae (Sheng Ma), 6 fen

Table 2
Analysis of the *Pí Wèi Lùn* “MS” clinical presentation. The correlation between the *Pí Wèi Lùn* possible “MS” clinical presentation⁷, and the Western medicine established MS signs and symptoms show a close correspondence.

Pí Wèi Lùn “MS” clinical presentation	Western Medicine established signs & symptoms of MS
Fatigue	Central fatigue – associated with demyelination of the central nervous system (CNS). 80% of the MS patients have fatigue, or more specifically lassitude ²⁴
Somnolence	Sleepiness – day time sleepiness that can often be mistaken by fatigue ³²
Debilitated limbs, Atonic flaccidity of the legs	Paresis, Paralysis
Insufficient essence spirit	Depression – the description may be referring to depression; 50% of the MS patients show depression, 36% show anxiety, 10% with pseudobulbar affect (PBA), and many others with mood swings. ²⁵ Dysthymia may also be present.
Cold inversion in the mornings and evenings, spontaneous sweating, feeling of Yin Qi shrouding the skin and hair (chills or a feeling of cold)	Autonomic nervous system dysfunction – MS lesions in the brain may affect thermoregulatory functions ^{29,30}
In the summer, original qi is damaged by intense heat, the fire-like heat coming back with the Yang Qi becoming effulgent when the sun is hanging high	Uhthoff’s symptom – Temporary (less than 24 h) and reversible worsening of neurological function in response to increase in core body temperature. 60–80% of MS patients experience temporary worsening of symptoms with heat exposure ¹⁸
Inability to taste food	Inability to distinguish the four taste qualities – taste deficits are associated with MS-related lesions throughout the brain. ³³ It can also, in rare cases, be due to Bell’s Palsy which occasionally affects MS patients ³³
Blurred vision, fire sparks emitted in the eyes	Optic neuritis (ON), nystagmus and diplopia are common issues in MS – ON may be present in 20% of the clinical isolated syndrome (CIS) cases, and it may develop in 50% of MS patients during the disease course ^{22,23}
Frequent urination	Bladder dysfunction – in a study, 65% of the MS patients reported urologic problems, and 79% reported urgent incontinence ³⁴
Difficult voiding of bound stools	Bowel dysfunction - Constipation affects 50% of the MS patients, and fecal incontinence also affect 50% at some point ³¹
Ventral pain in the cardiac region Obstruction in the chest	Cardiovascular dysfunction – MS patients present with a higher mortality rate that may be explained by increased cardiovascular risk and the presence of cardiovascular disease. ³⁵ The “obstruction in the chest” could be referring to chest tightness due to anxiety or coronary artery disease (CAD).
Flank pain or acute spasm, tightening below the umbilicus as if bound by ropes or, in extreme stabbing (lower abdominal) pain, difficulty relaxing the abdomen, pain in the upper and lower backs, scapulae and eyes	“MS hug” would be the equivalent to the flank pain and spasms. Pain – Overall, 50% of the MS patients experience pain that impacts quality of life. ²⁶ Abdominal pain may be due to thoracic demyelinating lesion. ³⁶ However, pain may be present in different places depending on where the demyelination happens in the central nervous system (CNS)
Frequent retching or dry retching or coughing with phlegm	Respiratory impairment – in a study with wheelchair-bound MS patients, 72.6% had impaired respiratory function with 61.1% of the patients presenting with cough. ³⁷ Regarding the retching, it is not a characteristic symptom of MS. It may be caused by additional factors such as stress or digestive problems that are frequently present in MS patients.
Foaming of the mouth	Seizures – Although rare, MS patients can have seizures. In a study, the incidence of seizures in MS patients was 3.5% compared to controls with 1.4%. ³⁸ Epilepsy is more common among patients with MS than in the general population, and MS increases the risk for seizures. ³⁸ This sign could refer to convulsive generalized seizures where foaming of the mouth is typically observed.
Frequent headaches	Headaches – a study found high prevalence of headaches in 78% of the MS patients studied. ²⁷ Another study reported 16.3% of MS patients with migraine, 23.5% with tension headache, none with cluster headaches, and 60.2% of the MS patients with headache remained unclassified. ²⁸
Rigidity of the tongue and inability to take food in easily	Dysphagia – in a study, 31.7% of the MS patients were classified as having dysphagia. ³⁹ In another study dysphagia was found in 34.3% of MS patients. ⁴⁰
Feeling satiated on eating, no desire to eat	Poor appetite

Radix Panacis Ginseng (Ren Shen), stemmed

Pericarpium Citri Reticulatae (Ju Pi), with the white inner skin preserved

Tuber Ophiopogonis Japonicae (Mai Men Dong), cored

Rhizoma Atractylodis (Cang Zhu), increases by 5 fen in the absence of sweating

Rhizoma Atractylodis Macrocephalae (Bai Zhu), 5 fen for each of the above

Cortex Phellodendri (Huang Bai), washed with wine to rescue the origin of water

Massa Medica Fermentata (Shen Qu), stir-fried, 3 fen (for each of the above

Radix Angelicae Sinensis (Dang Gui), washed with wine

Radix Praeparatus Glycyrrhizae (Zhi Gan Cao), 2 fen (for each of the above

Fructus Schizandrae Chinensis (Wu Wei Zi), 9 pieces”⁷.

The second formula that we mentioned in the present study is *Bù Zhōng Yì Qì Tāng (BZYQT 补中益气汤 “Tonify the Middle and Augment the Qi Decoction”)*. It is considered one of the most popular formulas from the *PWL* and widely used by clinicians in the treatment of autoimmune conditions. This formula appears on Chapter 2/Book 2 of the same *PWL* translation. This chapter, which precedes the one describing the “MS” pattern is entitled “*Treatise on Initiation of Heat in the Center Due to Damage by Food and Drink and Taxation Fatigue*”.⁷ *BZYQT* is composed of *Radix Astragali Seu Hedysari* (黄芪 *huáng qí*), *Radix Praeparatus Glycyrrhizae* (炙甘草 *gān cǎo*), *Radix Panacis Ginseng* (人参 *rén shēn*), *Radix Angelicae Sinensis* (当归 *dāng guī*), *Pericarpium Citri Reticulatae* (橘皮 *jú pí*), *Rhizoma Cimicifugae* (升麻 *shēng má*), *Radix Bupleuri* (柴胡 *chái hú*), and *Rhizoma Atractylodis Macrocephalae* (白术 *bái zhú*).⁷ Thus, *BZYQT* and *HQRST* have the same seven core herbs, and *HQRST* can be seen as a modification from *BZYQT* (Fig. 1). Throughout the *PWL*, *Li Gao* developed and

modified formulas to treat the different conditions that can arise from Spleen/Stomach Qi deficiency (or a deficit in the gastrointestinal system).⁷ According to the TCM diagnostic patterns, *BZYQT* “tonifies the Qi of the middle burner and raises sunken yang”.⁴³ Characteristic symptoms of the *BZYQT* diagnostic pattern include “intermittent fever, spontaneous sweating, aversion to cold, a thirst for warm beverages, shortness of breath, laconic speech, a tendency to curl up, weak limbs, pale complexion, loose and watery stools, pale tongue with thin white coating, a flooding-deficient pulse or deficient-rootless pulse in the middle”.⁴³ In contrast, *HQRST* not only tonifies the spleen/stomach Qi and raises the yang, but it also has the functions of the additional herbs. *Phellodendri cortex* (黄柏 *huáng bǎi*) resolves fire-toxicity and drains damp-heat in the lower burner, *Ophiopogonis radix* (麦门冬 *mài mén dōng*) nourishes the Yin of the spleen/stomach and heart/lungs and clears heat, *Schizandrae fructus* (五味子 *wǔ wèi zǐ*) contains leakage of Qi, generates fluids and quiets the mind, and *Massa medicata fermentata* (神曲 *shén qū*) relieves stagnation and harmonizes the stomach.⁴⁴ Therefore, *HQRST* is able to deal with conditions that have more heat-damp-toxicity such as the believed “MS” pattern described in chapter 3. It is important to note that, the TCM herbal formulas do not treat according to the Western diagnosis of diseases. They are prescribed for the TCM patterns of disease differentiation. Thus, *BZYQT* and *HQRST* could both be used for MS depending on individual manifestations and stage of the disease.

3.2.1. Single herbs and isolates

We found no clinical trials on *BZYQT* and *HQRST* for the treatment of MS/EAE. Our search indicated only one case study on the use of *BZYQT* for the management of IFN- β -induced flu-like symptoms in an MS patient.⁴⁵ However, twenty four studies were found on the hierarchically most important herbs that compose the two herbal formulas, and which were used for EAE. Upon examining the bibliographical references of each article found, we uncovered one paper that investigated the use of *berberine* (BBR) for EAE/MS.⁴⁶ Since one of the herbs of *HQRST* contains high concentrations of this isolate, we expanded our search to include *berberine* as a keyword. Thus, our search revealed studies on four herbs: *Astragalus radix* (黄芪 *huáng qí*), *Ginseng radix* (人參 *rén shēn*), *Glycyrrhizae radix* (甘草 *gān cǎo*), and *berberine* (BBR) containing *Phellodendri cortex* (黄柏 *huáng bǎi*).

Six papers were found on different forms of the broadly used TCM herb *Astragalus membranaceus* Bunge (黄芪 *huáng qí*) and its application on EAE.^{47–52} *Astragaloside IV* (ASI-IV) is a saponin, and the main active substance isolated from the *Astragalus* (黄芪 *huáng qí*).⁵³ Seven studies were retrieved specifically on the use of *Ginseng* for EAE.^{54–60} *Ginseng* can be classified according to their countries of origin: *Panax ginseng* or Korean *Ginseng* (人參 *rén shēn*), *Panax japonicus* or Japanese *ginseng*, *Panax notoginseng* or Chinese *ginseng* (三七 *sān qī*), *Panax quinquefolius* or American *Ginseng* (西洋参 *xī yáng shēn*), and *Panax vietnamensis* or Vietnamese *ginseng*.⁶¹ In general, the plants of the genus *Panax* have important pharmacological activities attributed to its main active principle, a saponin, known as *ginsenoside*. A number of 112 *ginseng* saponins were isolated from *P. ginseng* (人參 *rén shēn*) with less than ten of the *ginsenosides*, Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1 as the most abundant saponins.⁶¹ *Ginsan*, is a purified acidic polysaccharide (APG) extracted from *P. ginseng* (人參 *rén shēn*). Korean red *ginseng* extract or *Ginseng radix rubra* (KRG 红参 *hóng shēn*) is produced through a three-step process of washing, steaming and drying the fresh *P. ginseng* (人參 *rén shēn*).⁵⁸ Red *ginseng* is believed to have significantly higher biological effects and fewer side effects than the fresh-white *ginseng*.⁵⁸ The *ginsenoside* Rg3 is one of the most potent anti-inflammatory components of Korean red *ginseng* (红参 *hóng shēn*).⁶⁰ Although *P. ginseng* (人參 *rén shēn*) is used in the formulas

BZYQT and *HQRST*, we included in this review other species of *ginseng* used in controlled clinical trials that treated EAE/MS due to their similar pharmacological properties. We also found seven articles on *Glycyrrhizae radix* (甘草 *gān cǎo*), and its isolates which affected EAE.^{62–68} These isolates are *Glycyrrhizin* (GL) or *glycyrrhizic acid* (GA), 18- β -*glycyrrhetic acid* (GRA), and *Licochalcone A* (LicoA). GL or GA is a triterpenoid saponin extracted from *Glycyrrhiza glabra*. After oral consumption or intravenous injection, GL goes through hydrolysis by glucuronidase in the intestinal bacteria to form its main active principle aglycone, 18- β -*glycyrrhetic acid* (GRA).⁶⁹ LicoA is a chalcone that is extracted mainly from *Glycyrrhiza inflata*.⁷⁰ Also, a secondary search revealed four papers on *berberine* (BBR) that investigated its effects on EAE. BBR is a benzyl isoquinoline alkaloid, and one of the main active ingredients isolated from TCM herbs such as *Phellodendri cortex* (黄柏 *huáng bǎi*) and *Coptis rhizome* (黄连 *huáng lián*).⁴⁶

Ginseng radix (人參 *rén shēn*) and *ginsenosides* have shown protective effects on neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease and Amyotrophic Lateral Sclerosis (ALS).⁷¹ *Ginseng* has also been suggested as a candidate for the treatment of other autoimmune diseases such as Crohn's disease, ulcerative colitis, atopic dermatitis, and rheumatoid arthritis.⁷² The anti-inflammatory action of *ginseng*, among other properties such as anti-cancer, anti-microglial activation and anti-oxidant, may provide beneficial effects for chronic conditions such as cardiovascular diseases, cancer, diabetes, pulmonary diseases, anxiety, and depression.⁷³ *Astragalus radix* (黄芪 *huáng qí*) is considered anti-inflammatory, anti-oxidant, immune-modulatory, cardioprotective, hepatoprotective, neuroprotective, anti-tumor and anti-obesity.⁷⁴ It also inhibits liver fibrosis, stimulates blood regeneration, and has pain-relieving properties.⁷⁴ *Astragalus radix* (黄芪 *huáng qí*) has shown significant effects against diseases of the heart, brain, kidney, intestine, liver, and lungs, especially through anti-oxidant properties.⁷⁵ *Glycyrrhizae radix* (甘草 *gān cǎo*) also exhibits properties such as antibacterial, antiviral, antiprotozoal, anti-inflammatory, anti-oxidant, anti-diabetic and anti-tumor.⁷⁶ *Glycyrrhiza radix* (甘草 *gān cǎo*) has been researched with potential applicability for autoimmune conditions such as Behcet disease⁷⁷, rheumatoid arthritis⁷⁸, and diabetes.⁷⁹ *Phellodendri cortex* (柏黄 *huáng bǎi*) has a broad range of pharmaceutical actions such as anti-inflammatory, antimicrobial, antiviral, anti-tumor, anti-oxidant, antipyretic, antigout, antiulcer, anti-atopic dermatitis, and neuroprotective effects.⁸⁰ It has been studied for the use in meningitis, conjunctivitis, diarrhea, dysentery, jaundice, vaginal infections, enteritis, abscesses, and many other conditions.⁸¹ *Berberine* has shown promising results in the research of experimental autoimmune myocarditis, experimental autoimmune neuritis (the animal model of Guillain-Barré syndrome), and experimental-induced colitis.⁸¹ Thus, there is considerable potential for all these herbs to be used for chronic conditions and autoimmune diseases.

The effectiveness of the TCM herbal formulas is due, among other things, to their hierarchical organization. The formulations are composed of a chief, deputy, assistant and envoy herbs.⁴³ The chief herb treats the principal diagnostic pattern. The deputy supports the work of the chief herb or addresses a coexisting pattern. The assistant herbs reinforce the effect of the chief or deputy herbs, moderate toxicity or harsh effects of those herbs, or act as opposing assistants balancing the functions of the main component. The envoys drive the action to a particular channel or area of the body and harmonize the actions of the other herbs.⁴³ We were able to learn the hierarchy of *BZYQT*'s herbs from a bibliographical reference (Fig. 1).⁸² However, we could not locate any bibliography that could clarify *HQRST* herbal hierarchy. Some of *HQRST* herbal dosages are not listed in the PWL and modern interpretations of the

formula have different dosages.⁸² Regardless, it is clear that *Astragalus Radix* (黄芪 *huáng qí*) is the chief herb for both *BZYQT* and *HQRST*, and *Ginseng Radix* (人参 *rén shēn*) and *Glycyrrhizae Radix* (甘草 *gān cǎo*), are deputy herbs in *BZYQT*.⁴³ Also, *Ginseng Radix* (人参 *rén shēn*) occupies an elevated position in *HQRST* since it also composes the name of the formula. In *HQRST*, *Glycyrrhizae Radix* (甘草 *gān cǎo*) is on a lower position, but still important. Additionally, *Phellodendri cortex* (柏 *huáng bǎi*) renders an essential function to *HQRST*. Although only four herbs were reviewed here, they occupy vital positions in these formulas which demonstrates the importance of the findings for the purposes of our review (Fig. 1).

3.2.2. Mechanisms of action of the herbs/isolates on EAE

Four herbs present in *BZYQT* and *HQRST* showed synergistic and complementary properties on a variety of mechanisms of action affecting EAE. Improvement of EAE was due to the therapeutic intervention in different signaling pathways (Fig. 2). In general, the combination of these herbs/isolates provided a wide range of properties such as anti-inflammatory, anti-oxidant, anti-microglial activation, and anti-infiltration of inflammatory leukocytes. Some highlights about the actions of the herbs/isolates are worth mentioning here.

3.2.2.1. Anti-inflammatory and anti-microglial activation properties.

The activity of Th1/Th17 cells plays a central role in triggering the inflammatory response of EAE/MS, while the Treg cells have an immunosuppressive effect through the secretion of IL-10 modulated by the transcription factor Foxp3⁴⁸. Almost all the herbs/isolates studied are shown to have a regulatory effect on CD4⁺ T cells through the downregulation of Th1/Th17 cells, and upregulation of Treg cells. Also, most studies showed a decrease in the expression of pro-inflammatory cytokines such as TNF- α , IL-1 β , IFN- γ , IL-17 and IL-6, and adhesion molecules. In the study on the influence of the *Ginsenoside Rg3* on EAE, small effects on the secretion of IL-6, TNF- α and IL-12p40 from dendritic cells (DCs) were noticed.⁶⁰ However, the *ginsenoside Rg3* directly downregulated the expression of ROR γ t in CD4⁺ T cells which hindered Th17 differentiation from naïve precursors, and consequently alleviated Th17 mediated autoimmunity.⁶⁰ *Huang Qi* glycoprotein (HQGP), an extract of *Astragalus membranaceus Bunge* (AST 黄芪 *huáng qí*) by ammonium sulfate precipitation also delayed the onset and ameliorated the severity of EAE.⁵⁰ HQGP downregulated IL-6, IL-17, and TNF- α , but increased the expression of IFN- γ . The authors speculated that HQGP might have another mechanism of action different from other immunosuppressive agents through IFN- γ possibly improving EAE by limiting myelin peroxidation.⁵⁰ In this case, IFN- γ would have a protective role in EAE by regulating the removal of myelin debris by the antigen-presenting cells (APCs) in the CNS.⁵⁰ Also, HQGP inhibited the expression of CCL2 and CCL5 which consequently reduced the infiltration of inflammatory cells into the CNS of the EAE induced mice.⁵⁰ CCL2 and CCL5 are chemokines that promote adhesion of leukocytes to endothelial cells, which further stimulate activation and infiltration leading to demyelination and axon damage.⁵² The pathological overproduction of CCL5 is considered a sign of the MS disease progression.⁵⁰ An additional study also showed a downregulation of chemokines CCL2, CCL5 and CCR5 expression by HQGP.⁵² Moreover, *Astragalus polysaccharides* (APS) alleviated EAE through the upregulation of PD/PD-Ls pathway.⁵¹ The inhibitory receptor programmed death 1 (PD-1) expressed on the activated CD4⁺ and CD8⁺ T cells binds to the ligands PD-L1 and PD-L2 expressed on APCs.⁵¹ Then, PD-1 and PD-Ls negatively regulate the response of activated T cells. Thus, their upregulation led to a reduction of Th1/Th17 cell proliferation in the CNS and protected the brain tissue from injury. While APS decreased the expression of IFN- γ , TNF- α , IL-2, and IL-17, it did not

affect IL-4 and IL-10⁵¹. *Berberine* (BBR) also improved EAE induced mice through a novel mechanism seen in this isolate. BBR selectively inhibited the differentiation of Th17 cells and to a lesser degree Th1 cells through the JAK/STAT signaling pathway.⁸³ JAK/STAT pathways regulate T cell differentiation and their functions. BBR caused a decrease in the phosphorylation of STAT3 and ROR γ t expression in Th17 cells and mildly reduced expression of p-STAT4 and T-bet in Th1 cells.⁸³ Jointly, BBR reduced Th17/Th1 cells differentiation but showed no effect on CD4⁺ T Fox3⁺ Treg cells.⁸³

A reduction of neuroinflammation in all cases led to an amelioration of EAE with a decrease in leukocyte infiltration in the CNS, neuronal damage, and demyelination. Some studies point to microglial activation as the hallmark of demyelinating conditions such as MS/EAE. Less microglial activation may prevent the recruitment and transmigration of encephalitogenic T cells through the BBB into the CNS. GRA/GA, GR extract, and KRGE demonstrated the capacity of decreasing microglial activation.^{58,63,67} *Panax notoginseng* or NotoG TM (三七 *sān qī*) suppressed microglial activation, downregulated IL-6, TNF- α and NO which then promoted anti-inflammatory effects.⁸⁴ AST downregulated the expression of the hippocampal glial fibrillary acidic protein (GFAP) and CD11b⁺ cells, the astroglial and microglial markers in the CNS, respectively.⁴⁹ APG decreased CD4⁺ T cells and CD11b⁺ macrophages⁵⁷, and HQGP reduced the number of infiltrated CD11b⁺ monocytes, CD4⁺ T cells and CD68⁺ cells in the CNS.⁵² CD68⁺ is the surface marker of macrophages and activated microglia.⁵² Also, BBR revealed another means of improving EAE. BBR downregulated IL-6 producing CD11b⁺ cells, reduced the activity of NF- κ B, downregulated the surface expression of co-stimulatory molecules CD80⁺ and CD86⁺ in CD11b⁺ cells, and consequently decreased Th1/Th17 cell differentiation and function.⁸³

Another important mechanism refers to the ability of some herbs to modulate Th1/Th2 cell activity. While, for example, ASI-IV and APS did not affect Th2 cells^{48,51}, *ginsenoside Rd* promoted Th2 shift and contributed to an anti-inflammatory effect.⁵⁶ Another important mechanism that we learned refers to the high mobility group box 1 protein (HMGB-1). HMGB-1 is considered a damage-associated molecular pattern (DAMP) and acts as a pro-inflammatory cytokine.^{64,85} Since the intravenous administration of anti-HMGB-1 monoclonal antibody has been shown to suppress EAE progression, inhibition of HMGB-1 may be a potential therapy for EAE/MS.⁶⁵ GL exhibited anti-inflammatory properties by blocking HMGB-1, decreasing demyelination, and improving EAE.^{64,65}

3.2.2.2. Anti-oxidant effects and the Blood-Brain Barrier (BBB).

In MS, high levels of reactive oxygen species (ROS) are present which leads to the breakage of the BBB.⁴⁷ Increased permeability of the BBB allows the infiltration of leukocytes into the brain and consequently promotes neuroinflammation and demyelination. AST/ASI-IV can counteract oxidative stress by decreasing ROS and increasing anti-oxidant enzymes which then reduce BBB permeability.^{47,49} This diminishes leukocyte infiltration and ameliorates neuroinflammation and demyelination.⁴⁷ Oxidative stress can also cause direct damage to the myelin sheath, and LicoA has been seen to have antioxidant properties that counteract this injury.⁶² Additionally, GRA/GA also has anti-oxidant properties through the decrease of thiobarbituric acid reactive substances (TBARS), and an increase of antioxidant system, both enzymatic (SOD, CAT, and GRx), and non-enzymatic (GSH).⁶⁶ Since BBB disruption is a big issue in MS, herbs/isolates that influence BBB by decreasing permeability and/or restoring barrier function are of great value. Other herbs can also reduce BBB permeability such as KRGE (红参 *hóng shēn*)⁵⁸, and *ginsenoside Rd*.⁵⁶ Additionally, ginseng is lipophilic and crosses biological membranes⁵⁶, which adds another

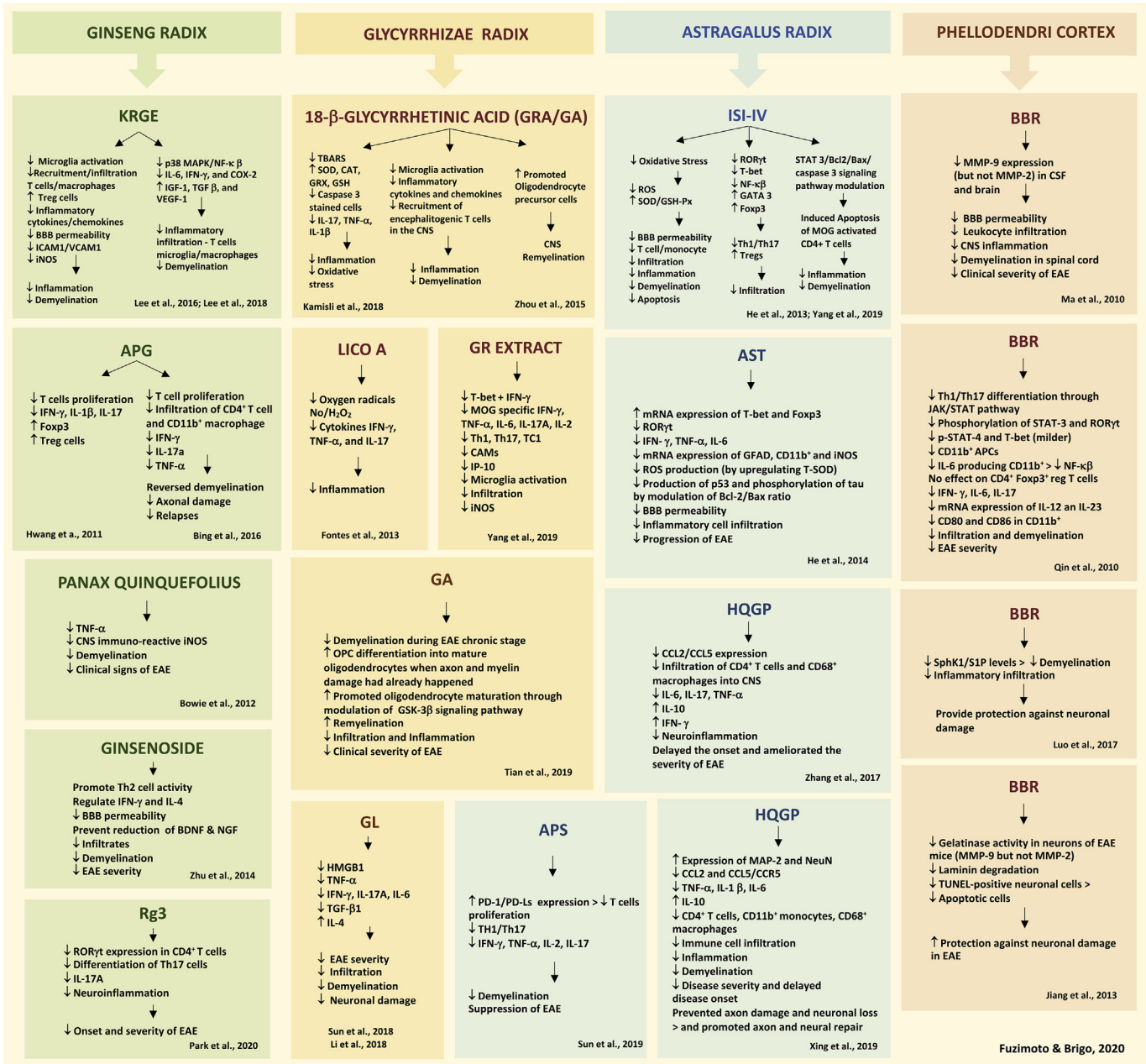


Fig. 2. The effect of *Astragalus radix* (黄芪 huáng qí), *Glycyrrhiza radix* (甘草 gān cǎo), *Ginseng radix* (人參 rén shēn) and *berberine containing Phellodendri cortex* (黄柏 huáng bǎi) on EAE induced mice. Twenty four studies on the hierarchically most important herbs/isolates contained in *Bù Zhōng Yì Qì Tāng* 补中益气汤 “Tonify the Middle and Augment the Qi decoction”) and *Huáng Qì Rén Shēn Tāng* (黄芪人參湯 “Astragalus and Ginseng decoction”) showed an improvement of EAE, neuronal damage and demyelination through different signaling pathways and mechanisms of action which are synergistic and complementary.

attractive reason for its use for EAE/MS.

Another mechanism worth highlighting here is the specific action of *berberine* (BBR) on the improvement of EAE.⁴⁶ BBR reduced the activity of the gelatinase metalloproteinase 9 (MMP-9) in the brain and CSF of EAE mice which caused a decrease of BBB permeability and consequently inhibited leukocyte infiltration into the CNS.⁴⁶ MMP-9 and MMP-2 are enzymes present in the extracellular matrix (ECM) that control cell migration across the BBB. Increased MMP-9 and MMP-2 can specifically degrade type IV collagen, a component of the basement membrane that surrounds the blood vessels, disrupt BBB and allow the transmigration of T cells.⁴⁶ So, the downregulation of MMP-9 and MMP-2 is protective against EAE/MS. However, the expression of MMP-2 was not

decreased in this study, and the authors theorized that MMP-2 could have a protective effect by remodeling the extracellular matrix, especially in the progressive stage of MS.⁴⁶

BBR also showed an improvement of EAE through the downregulation of the sphingosine kinase 1 (Sphk1)/sphingosine 1-phosphate (S1P) receptor signaling pathway in astrocytes.⁸⁶ SphK1/S1P upregulation has been reported in MS, and the severity of EAE/MS correlates to the degree of gliosis. Inhibition of gliosis may improve EAE/MS. Since astrocytes give support to the BBB, a downregulation of SphK1/S1P may decrease BBB permeability and inflammatory infiltration.⁸⁶ To complete some of its beneficial aspects, BBR can cross the BBB and has neuroprotective and neurotrophic properties.⁸⁷

3.2.2.3. Apoptotic/anti-apoptotic balance, and neuronal protection. ASI-IV induced apoptosis of MOG specific CD4⁺ T cells in EAE while protecting neurons from dying.⁴⁸ This is imperative because the promotion of apoptosis of inflammatory cells without harming neurons is a big challenge in the treatment of MS especially during the use of pharmaceutical drugs.⁶⁷ In another study, *Astragalus membranaceus* Bunge (AST 黄芪 huáng qí) modulated Bcl-2/Bax ratio and inhibited the production of the pro-apoptotic p53 and tau phosphorylation.⁴⁹ Bcl-2/Bax ratio is used to evaluate apoptotic tendency of cells, and phosphorylated tau is one of the indicators of neuronal damage.⁴⁷ Ginsenoside Rd prevented the reduction of the brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), important neurotrophins in protecting tissue damage in EAE.⁵⁶ Neurotrophic factors may be responsible for the pathogenesis of neurodegenerative conditions, and neurotrophic agents have been used to support neuronal function in MS.⁸⁸ Additionally, BBR decreased MMP-9 gelatinase activity which reduced the degradation of the ECM laminins, which then halted the induction of neuronal apoptosis.⁸⁹ Laminins are major proteins of the ECM that participate in neuronal development, survival, and regeneration. Laminin degradation was associated with MMP-9 activity and MS disease severity, and its reduction was shown to improve EAE.⁸⁹ As a consequence of the reduction of MMP-9 and laminins, there was a restoration of BBB, decreased lymphocyte infiltration and cytokines/chemokines expression, which then provided protection against neuronal damage.⁸⁹

3.2.2.4. Effects on the myelin sheath. We saw four effects on myelin in the studies. All the studies showed a reduction in demyelination once the neuro-inflammation was controlled by the herbs/isolates. Second, whereas there were dramatic axon damage and neuron loss in the spinal cord of EAE induced mice, HQGP protected mature neurons from inflammation and cell death, and neuronal axon from damage by increasing MAP-2 and NeuN.⁵² The microtubule related protein-2 (MAP-2) is used as a marker of neuronal axons. The neuron nuclear antigen (NeuN) is a specific marker of mature neurons and reflects their damage and repair.⁵² Thus, besides decreasing demyelination, HQGP protected and prevented the damage of both axons and neurons in the CNS. Third, APG reversed demyelination and the progression of axonal damage in relapsing-remitting EAE.⁵⁷ In this case, APG induced remission of demyelination and axonal damage.⁵⁷ Fourth, GRA/GA caused a proliferation of oligodendrocyte precursor cells (OPCs) which promoted remyelination.⁶³ Furthermore, in another study, besides inhibiting demyelination and reducing further myelin damage in EAE, GA caused the differentiation of OPCs and their maturation into oligodendrocytes (OLGs) in vivo and in vitro via GSK-3 β modulation signaling pathways.⁶⁸ GA promoted myelin basic protein (MPB) and remyelination during the chronic stage of EAE when axonal damage and neuronal loss are already established.⁶⁸ The stimulation of OPCs differentiation and maturation is critical for myelin repair, and one action that DMTs are unable to perform. Herbal compounds with a variety of herbs have the potential to address multiple signaling pathways implicated in MS and increase the chances of a successful treatment.

3.3. Additional considerations on TCM herbs for MS

In a systematic review that included studies in the Chinese language, twenty studies on Chinese herbal medicine for Relapsing-Remitting Multiple Sclerosis (RRMS) were evaluated.⁹⁰ The top five most used herbs were *Angelica sinensis* radix (当归 dāng guī), *Glycyrrhizae radix* (甘草 gān cǎo), *Paeonia rubra* radix (赤芍 chì sháo), *Rehmanniae preparata* radix (熟地黄 shú dì huáng), and *Bombycistrictatus* (僵蚕 jiāng cǎn). This meta-analysis showed a

significant effect of the TCM herbs in improving expanded disability status scale (EDSS) ($P < 0.01$), annual relapse rate ($P < 0.01$), and total clinical efficacy rate ($P < 0.01$) of the MS subjects when compared with the western conventional treatments.⁹⁰ The other herbs found to be frequently used for MS were *Radix astragali seu hedydari* (黄芪 huáng qí), *Herba epimedii* (淫羊藿 yín yáng huò), *Scorpio* (全蝎 quán xiē), *Semen coicis* (薏苡仁 yì yǐ rén), *Achyranthis bidentatae radix* (牛膝 niú xī), *Poria* (茯苓 fú líng), *Pinelliae rhizome* (半夏 bàn xià), *Semen Cuscuta* (菟丝子 tù sī zǐ), *Atractylodes Macrocephalae rhizome* (白术 bái zhú), *Ligustici rhizome* (川芎 chuān xiōng), *Rehmanniae recens radix* (生地黃 shēng dì huáng), *Herba cistanches* (肉苁蓉 ròu cōng róng), *Arisaematis cum bile* (胆南星 dǎn nán xīng), and *Lumbicus* (地龙 dì lóng).⁹⁰ Four of the herbs in this complete list are included as core herbs of BZYQT and HQRST (Fig. 1). The present study does not intend to imply that these two formulas could be the best or only choices that may influence EAE/MS. The practice of TCM requires an individual diagnostic evaluation to determine the best herbal treatment approach. Also, in the PWL, BZYQT and HQRST are modifiable with herbal additions and subtractions according to the individual symptomatology and stage of disease.

The Chinese herbal formulations are based on a very sophisticated medical system that considers multiple factors. Although the study of the herbs/isolates may point to the potential development of individual pharmaceutical drugs for MS, we need to consider the benefits of compounds that address multiple signaling pathways involved in MS. TCM herbal formulas are strategically designed to deliver multiple active principles through an herbal synergistic and complementary approach while counteracting excesses, relieving toxicities, protecting internal organs, and minimizing side effects. The four herbs/isolates researched here do not represent all the pharmaceutical properties that they possess. They are just a snapshot of what they could deliver for the MS care. Further high quality randomized controlled clinical trials are necessary to inform clinical practice and determine the effects of TCM herbs in slowing disease course. The water extract of *KRGE* (红参 hóng shēn) and *P. quinquefolius* (西洋参 xī yáng shēn), and the alcohol extract of *GR* showed significant improvement of EAE.^{55,58,59,67} While ASI-IV significantly attenuated the deterioration of EAE, the AST ethanol extract showed a stronger effect when compared to ASI.⁴⁹ This suggested that AST may contain other ingredients that can synergistically alleviate EAE/MS.⁴⁹ Therefore, more investigations are required to determine the advantages and disadvantages of the herbs' mode of delivery, for example whole herb extract vs. isolates. Also, in the majority of the studies, the improvement of EAE was obtained through a dose-dependent administration of the herbs/isolates. Therefore, further research is also necessary to investigate the herbal concentrations and dosages that would slow the disease course of MS patients.

3.4. MS and the gastrointestinal function

The MS clinical presentation in the PWL is described under a diagnostic pattern of differentiation of spleen and stomach Qi deficiency. Thus, the PWL clearly established a connection between the believed MS and the gastrointestinal function.⁷ *Li Gao* also recommended that one presenting with such signs and symptoms should refrain from consuming wine, wheat ("sodden wheat food"), spices and eating too much cold food. These could impair digestive function and worsen the disease. Therefore, according to *Li Gao*, nutrition is of utmost importance for "MS".⁷ The connection between the gastrointestinal system and the neuro-immunological symptoms has been well established in TCM physiopathology since at least the Han dynasty.⁹¹ In TCM, the intestines are considered a second brain. It is not a coincidence that recent biomedical research has shown a renewed interest in

understanding the interdependence between the brain and gut.

3.4.1. MS and the “microbiome-gut-brain” axis

The brain-gut axis is modulated by the autonomic nervous system (ANS), peripheral peptides, regulatory proteins, and neurotransmitters that influence the central nervous system (CNS).⁹² The CNS and the gastrointestinal system generate and respond to a series of same peptides and regulatory proteins that allow the interaction between them, and the BBB acts as an interface of the brain-gut axis.⁹³ An increasing number of studies are now linking gut problems such as an increased permeability of the intestinal barrier to autoimmune conditions.^{94–97} The theory of altered permeability of gut lining has been investigated as an influential factor of the MS pathogenesis.^{98,99} Evidence shows that MS patients have increased intestinal permeability, alterations in the gut microbiome, and changes in the metabolism of bile acids.¹⁰⁰ The gut microbiome participates in the modulation of the immune system, metabolic functions, production of neurotransmitters, and it also plays a role in the development of the hypothalamus-pituitary-adrenal (HPA) axis.¹⁰¹ Experiments on the involvement of commensal microbiota and the development of EAE point out that these microorganisms may be involved in the development of MS through the “microbiome-gut-brain” axis.¹⁰² In fact, some studies believe that the gut microbiome may be the main environmental factor mediating CNS demyelination in MS.^{103,104} The “microbiome-gut-brain” axis integrates different theories that may be involved in the MS pathogenesis. Genetic factors, environmental determinants such as hygiene and sanitation, the use of antibiotics, vaccination, diet and lifestyle factors may contribute to causing intestinal dysbiosis.¹⁰⁵ Then, gut dysbiosis influences the intestinal barrier and BBB integrity, and promotes changes in the microbiota pro-/anti-inflammatory responses.¹⁰⁵ Thus, the “microbiome-gut-brain” axis is a bidirectional informational network that involves the gut microbiota and their metabolic products, and an array of systems such as autonomic nervous system, neural-immune system, neuroendocrine, enteric nervous system, and central nervous system.¹⁰⁶

An extensive amount of literature has been published on nutrition and dietary supplementation for MS. Recent research showed preliminary evidence that dietary factors influence the MS incidence, disease course, and symptomatology.¹⁰⁷ Among the most common subjects studied concerning MS and nutrition, we found the Paleolithic diet, Mediterranean diet, “Western diet”, fats, dairy, vitamin D, diet quality, caloric restriction, and fruits, vegetables, and grains.¹⁰⁷ Nutritional interventions can affect EAE/MS, for example, through an anti-inflammatory and anti-oxidant actions.^{108,109} Dietary habits play a role in the susceptibility and increased risk of EAE, and changes in diet modify the gut microbiome and ultimately affects the immune system.¹⁰¹ Therefore, the recent research trend on MS centered in the “microbiome-gut-brain” axis seems to validate *Li Gao*'s view on the connection between gastrointestinal and neuro-immunological functions.

3.4.2. TCM herbs and the gut microbiota-microbiome in MS patients

A healthy diverse gut microbiota and its resultant balanced metabolic pathways are essential for an appropriate intestinal function and immune homeostasis.¹¹⁰ The majority of studies on MS and microbiota has concentrated on bacteria or bacteria and archaea, and not as much on viruses and fungi.¹¹⁰ Studies suggest that MS patients have dysbiosis with depletion of certain bacteria that are able to induce an anti-inflammatory response, and have an abundance of other bacteria that promote pro-inflammatory reactions.¹¹⁰ This knowledge could be used in the treatment of MS. For example, some organisms have been seen to alleviate the

severity of EAE such as *Bifidobacterium animalis*¹¹¹, a mixture of *Lactobacillus spp.*¹¹², and the polysaccharide A (PSA) produced by *Bacteroides fragilis*.^{113,114} *Prevotella histicola* provided immunomodulatory capabilities in EAE by downregulating Th1/Th17 cells, increasing the frequency of CD4⁺ Foxp3⁺ regulatory cells, tolerogenic dendritic cells, and suppressive macrophages.¹¹⁵ However, it is important to note that there is not an “MS-associated gut microbial signature”, and the interpretation of the microbiome in MS patients is still under debate.¹¹⁶

TCM herbs modulate the gut microbiota to recover ecological balance, and on the other hand, the microbiota regulates the conversion-absorption-reversion processes of the herbs in the gut.¹¹⁷ Some studies have highlighted the potential prebiotic effects of medicinal herbs to support digestion and bio-absorption. They have also suggested that the health benefits of herbs are in part due to their ability to modulate the gut microbiota in a way that reduces inflammation, improves colonic epithelium, and prevents opportunistic infections.^{118,119} The gut microbiota can alter the transformation and absorption of ginsengs¹²⁰, but ginsengs can also modify gut microbiota. Ginseng extract increased *Proteobacteria*, *Methylobacteriaceae*, *Parasutterella*, *Sutterella*, and the probiotics *Bifidobacterium* and *Lactobacillus*. These last two rendered an anti-inflammatory effect through upregulation of IL-4 and IL-10.¹²¹ Another study was able to show that long term administration of ginseng extract significantly increased probiotics *Bifidobacterium*, *Lactobacillus*, *Allobaculum* and *Clostridium* while downregulating pathogenic bacteria such as *Butyrivimonas*, *Parabacteroides*, *Alis-tipes*, and *Helicobacter*.¹²² Also, red ginseng (红参 *hóng shēn*) promoted the growth of *Lactobacillus* and *Bifidobacterium*, and at the same time inhibited the proliferation of bacterial pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella spp.*¹²³ In an animal model, *Astragalus* (黄芪 *huáng qí*) also increased *Lactobacillus* and affected fecal microbial composition.¹²⁴ *Glycyrrhiza radix* (甘草 *gān cǎo*) significantly increased *Bacteroides spp.*, among other bacteria, and reduced *Eubacterium spp.* while also decreasing opportunistic pathogens such as *Enterococcus faecalis* and *Klebsiella pneumoniae*. In an animal model, *berberine* modulated gut microbiota and inhibited LPS-induced TLR-4/TNF- α activation which resulted in a reduction of insulin resistance.¹²⁵ Thus, the herbs that compose the formulas for “MS” described in the *PWL* could have a far-reaching action on the immune system modulation, and the healing of MS. Some herbs have very low bioavailability, and the action of the herbs through the microbiome offers another explanation for their role in modulating the immune system.¹¹⁷ Further research is necessary to evaluate the influence of the TCM herbs on the microbiota and the epithelial lining healing of MS patients.

4. Conclusion

Our review proposes that the medical treatise, the *Pí Wèi Lùn*, written by the physician and scholar *Li Gao* (1180–1251 C.E.) during the *Jin-Yuan* dynasties (1115–1368 C.E.) in China is the first record of MS in the medical literature. To support our claim, we investigated the believed “MS” clinical presentation described in the *PWL*, and the herbal formulas and single herbs used for it. Two *PWL* main formulas are used for this disease description, *BZYQT* and *HQRST*. Twenty four studies on the hierarchically most important herbs/isolates in these formulas which treated EAE were located. All the herbs/isolates showed a significant improvement in EAE, neuronal damage, and demyelination. Collectively, the herbs/isolates reduced the severity of EAE through intervening in different signaling pathways and using different mechanisms of action. These herbs provided a wide range of properties such as anti-inflammatory, anti-oxidant, anti-microglial activation, anti-infiltration of inflammatory leukocytes in the CNS, apoptotic/anti-

apoptotic balance, and neuronal protection. Overall, these herbs promoted a downregulation of Th1/Th17, and upregulation of Treg cells. The BBB permeability was normalized due to the improvement of neuro-inflammation and the anti-oxidant properties. The herbs also showed the ability to decrease and reverse demyelination, and two herbs caused remyelination. Our findings help us contemplate the possible beneficial applications of these *PWL* formulas since all herbs caused an improvement of EAE, and could potentially offer invaluable support to MS. The *PWL* offers a fertile area of research for the treatment of MS.

Li Gao inaugurated a new era of internal medicine in China.⁴² Neurological conditions such as MS were already considered multi-factorial by Chinese medicine doctors, and *Li Gao's* strategy also had a preventive approach through strengthening the terrain. He strategized the diagnosis and treatment of diseases as having the central key element of the spleen-stomach *Qi*, or the gastrointestinal function. Not coincidentally, biomedical research has experienced a renewed interest in the "microbiome-gut-brain" axis and its involvement in autoimmune diseases such as MS. The connection between gut-nutritional habits and neuro-immunological function was already known by physicians and scholars since at least the *Han* dynasty (206 B C E – 220 C E).⁹¹ While DMTs are still the standard of care for MS, research has been demonstrating an enormous potential of TCM herbal remedies for the treatment of this disease. Future studies should explore, among other factors, the properties of the whole formulas and their involvement in the different signaling pathways of MS, the cooperative and harmonizing action of herbs in those formulas, and the advantages-disadvantages of the whole herb extracts vs. isolates. It is also important to study the dose-dependent action of the herbs for MS and other autoimmune conditions. TCM herbal medicine may potentially alleviate the pathogenesis and slow disease course of MS, but future high quality randomized controlled clinical trials are necessary to better inform clinical practice.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ADF conducted the whole research, wrote the article in its entirety including the historical review, the traditional Chinese medicine (TCM) and Western medicine aspects of the manuscript, the immunological analysis of the herbs, and designed the tables and figures. FB contributed to the analysis of the clinical presentation of the *Pí Wèi Lùn* and the Western diagnosis of MS, and revised the paper.

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Declaration of competing interest

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