International Immunopharmacology 67 (2019) 87–97

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Natural products: Potential therapeutic agents in multiple sclerosis

Shuangwen Yu[a,b], Mei Liu[b,*], Kaili Hu[a,c,*]

[a] Murad Research Center for Modernized Chinese Medicine, Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

[b] Shanghai Innovation Center of TCM Health Service, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

[c] Key Laboratory of Smart Drug Delivery, Fudan University, Ministry of Education, Shanghai 201203, China

ARTICLE INFO

Keywords:
Multiple sclerosis
Natural products
Anti-inflammatory
Immune regulation
Neuroprotection
Nervous system repairing

ABSTRACT

Multiple sclerosis is an autoimmune neurodegenerative disease, which usually caused by inflammation, demyelination, and axonal injury. The currently available medications for multiple sclerosis do not directly promote myelin sheath repair. Therefore, many researches have attempted to achieve better therapeutic effects through promoting remyelination. Natural products not only alleviate clinical symptoms, but also have the unique advantages of protecting and repairing effects on nervous system. We here present a systematic review on published papers about treating multiple sclerosis by natural products, aiming to provide comprehensive information on natural products in the treatment of multiple sclerosis.

1. Background

Multiple sclerosis (MS) is a chronic inflammatory and diffuse neurodegeneration disease of the central nervous system (CNS) with primary demyelinating in the gray and white matter of the brain and spinal cord [1]. According to where the inflammatory invasion arises in the CNS, the clinical symptoms of MS may include visual, motor, sensory disturbances, and autonomic disturbances of bowel and bladder [2]. In addition, inflammatory cells which pass through the blood-brain barrier (BBB) and invade the CNS in MS resulting in demyelination and edema [3]. About 80% of MS patients are attacked by relapsing-remitting MS, which is characterized by a long period of remission after the attack. Then after a few years, most of patients' conditions change from relapsing-remitting MS to secondary-progressive MS. While patients of primary-progression MS don't experience the periods of recurrence and remission, the disease deteriorates continuously from the onset of the first attack [4]. Current marketed drugs for MS include injectable formulations like interferon beta, glatiramer A and natalizumab as well as oral medicines like fingolimod, teriflunomide, and dimethyl fumarate [5–7]. All these medicines are primarily for correcting abnormal autoimmune responses and inhibiting inflammation. No medication fully prevents or reverses the progressive neurologic deterioration [8]. Since the regulation of peripheral inflammatory responses and demyelination can't stop neuronal loss, the current treatment is still at a lower level of relieving symptoms temporarily [3]. Therefore, in the treatment of MS, it is of great significance to promote the repair of damaged nerve tissue, correct abnormal immune responses and inhibit inflammation. Natural products (NPs) as a huge treasure, exhibit unique advantages in the regulation of immune system, anti-inflammatory, as well as protection and repairment of the CNS. This paper summarizes the various effective mechanisms of NPs in the treatment of MS in hope to provide reference for further improving the treatment of MS by NPs.

2. Anti-inflammatory and immunomodulatory

2.1. Effects on the induction stage of autoimmune response

T cell-mediated cellular immunity which mainly including T helper cell (Th)1/Th2, Th17 and regulatory T cells (Tregs) is involved in the pathology of MS [9,10]. Th1 and Th2 differentiated from CD4+ cells have opposite functions and cytokine secretion patterns. Th1 secretes cytokine IL-2, IL-3, IFN-γ, TNF-α, which produce inflammatory responses in the CNS, and cause MS [11,12]. Th2 secretes IL-4, IL-5, IL-6, IL-10, IL-13, TGF-β, which have ability to inhibit the proliferation of Th1 [11,13]. Therefore, the balance of Th1/Th2 plays an important role in maintaining the homeostasis of the immune system, thus controlling the inflammatory reaction *in vivo*. Th17 cells secrete IL-17, IL-6, IL-21

* Correspondence to: M. Liu, Shanghai Innovation Center of TCM Health Service, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China. K. Hu, Murad Research Center for Modernized Chinese Medicine, Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China.

E-mail addresses: liumeiy@aliyun.com (M. Liu), kaili-hu@163.com (K. Hu).

https://doi.org/10.1016/j.intimp.2018.11.036
Received 10 September 2018; Received in revised form 19 November 2018; Accepted 21 November 2018
Available online 08 December 2018
1567-5769/

and IL-22, which involved in inflammation and autoimmune disease. Th17 can also secrete IFN-γ and IL-4 which inhibit CD4+ cells to differentiate into Th17 [14]. Tregs play an important role in maintaining immune system normalization, and the immunosuppressive level of Tregs is closely interrelated with its activity and quantity [9,15]. Foxp3, known as forkhead/winged helix transcription factor, plays an important role in regulating the development of Tregs [16,17]. When the proportion of Tregs is decreased, the expression of transcription factor Foxp3 is decreased, and the activation ability of T cells is suppressed [18]. Moreover, spleen as the largest immune organ, can participate in the immune response *in vivo*. When spleen monocytes were inhibited to secretory inflammatory factors IL-17, the inflammation will be reduced. In addition, chemokines can attract various types of leukocytes to sites of infection and inflammation, and regulate their trafficking [19,20]. The most critical chemokines are CXC chemokine ligand-10 (CXCL10) and chemokines chemokine ligand-2 (CCL2) which is also referred to as monocyte chemoattractant protein 1 (MCP-1). CCL2 can regulate monocytes/macrophages and T cells while CXCL10 can regulate many cell subsets including T lymphocytes, both are chemoattractant and play a crucial role in the recruitment and accumulation of inflammatory cells [21]. The detailed mechanism of effects on the induction stage of autoimmune response was shown in Table 1.

2.1.1. Icariin

Icariin, isolated from the natural plant *Epimedium* family, has been proved with various pharmacological activities. To confirm effects of icariin on the autoimmune demyelinating, experimental autoimmune encephalomyelitis (EAE) mice was treated with icariin (purity > 98%) by orally administered at a dose of 25 mg/kg at the pre-symptomatic stage. The clinical score decreased, and symptoms improved. Further research revealed that quantities of Th1 and Th17 cells in the lymph nodes and splenocytes were decreased, as well as ratio of Th17 cells in CNS monocytes. The proliferation of T cells and differentiation of Th1 and Th17 were inhibited, which may be mediated *via* modulation of dendritic cells [22].

2.1.2. Plumbagin

Plumbagin is the main active chemical of traditional herb *Plumbago zeylanica* Linn. To test the protective effects of plumbagin on EAE mice, plumbagin was administered by intraperitoneal injection at a dose of 2 mg/kg before induction of EAE. The results show that plumbagin can ameliorate clinical symptoms of EAE (including inflammation and demyelination of the CNS) and inhibit the differentiation, mature and normal function of human monocyte derived dendritic cells. *In vivo* and *in vitro* experiments showed the mRNA expression of TNF-α, transforming growth factor beta (TGF-β), IL-1β, IL-6, IL-12, and IL-23 have been inhibited by plumbagin in dendritic cells, which may be associated with the differentiation of Th1 and Th17 cells [23].

2.1.3. Apigenin

Apigenin is a chemical presented in various plants like fruits, vegetables, herbs and spices. Apigenin was administered by oral gavage at a dose of 40 mg/kg at the pre-symptomatic stage of EAE. Apigenin can delay the development of EAE, alleviate the severity and clinical score of EAE as well as restore the body weight of EAE mice to normal. Apigenin exerted these effects by decreasing Th17 quantity, increasing regulatory T cell quantity and promoting the restoration of T cell function of EAE mice. The spinal cord slices analyzed by hematoxylin-eosin staining showed a reduction of infiltrated inflammatory cells. What's more, an analysis of brain cells isolated from EAE mice show that the number of CD45+/CD68+ cells decreased significantly [24]. So apigenin possesses the activity of reducing inflammation and infiltration of immune cells into the CNS.

2.1.4. Salvianolic acid B

Salvianolic acid B is active chemical of the traditional Chinese herb *Salvia miltiorrhiza*. After administering 30 mg/kg salvianolic acid B to mice at the symptomatic stage of EAE, inflammatory cells were inhibited from infiltrating into the CNS, astrocytes and microglia/microphage amount was reduced in CNS and the disease severity decreased. Salvianolic acid B treatment can also prevent from body weight loss. In addition, Th1 cell population was specifically suppressed and the concentration of IFN-γ was significantly decreased by salvianolic acid B both *in vivo* and *in vitro*. Besides, salvianolic acid B exerted a strong suppressive effect on peripheral CD4+ T cells *in vivo* [25].

2.1.5. Eriocalyxin B

Eriocalyxin B is a diterpenoid isolated from *Isodon eriocalyx* which was used for anti-inflammatory. Following intraperitoneal injection of eriocalyxin B (purity > 99%) with 10 mg/kg to mice before induction of EAE, the results showed that eriocalyxin B alleviated symptoms and delayed MS onset, and reduction of CNS inflammation and demyelination was detected by histological analysis of spinal cord tissue. In addition, autoreactive T cells were unable to transfer and CD4+ and CD11b+ cell populations were decreased after treatment with eriocalyxin B. Most importantly, eriocalyxin B can inhibit Th1 and Th17 cell differentiation through Jak/STAT and NF-κB signaling pathways as well as elevation of reactive oxygen species [26].

2.2. Effects on CNS inflammation

MS is a chronic inflammatory demyelinating disease of the CNS, and usually reflects on inflammatory mediators and inflammatory cells infiltrating into CNS, which will cause brain damage and nerve dysfunction [27]. Over expression of inflammatory mediators lead to local demyelinating plaques, and then cause different degrees of neurological dysfunction. Therefore, the elimination of inflammation is of great significance to MS patients. Reducing inflammation temporarily will decrease the infiltration of inflammatory mediators and inflammatory

Table 1
NPs with effects on the induction stage of autoimmune response.

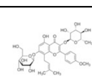
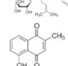
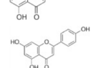
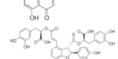
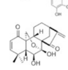
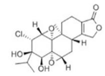
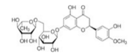
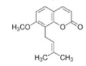
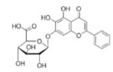
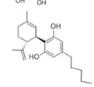
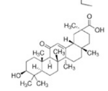
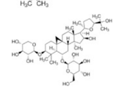
Compound name	Source	Structure	Dose	Animal strains	Model	Mechanism
Icariin [22]	*Herba epimedii*		25 mg/kg *i.g.*	C57BL/6 mice	Chronic EAE	↓ Th1, Th17
Plumbagin [24]	*Plumbago zeylanica*		2 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ Th1, Th17
Apigenin [25]	Fruits, vegetables, herbs, spices		40 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ Th1, Th17
Salvianolic acid B [26]	*Salvia miltiorrhiza*		30 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ Th1,IFN-γ
Eriocalyxin B [27]	*Isodon eriocalyx*		10 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ Jak/STAT pathway; ↓ NF-κB signaling

Table 2
NPs with effects on CNS inflammation.

Compound name	Source	Structure	Dose	Animal strains	Mosel	Mechanism
Tripchlorolide [29]	*Tripterygium wilfordii*		40 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ (T-bet, RoRγt; IFN-γ, IL-17)
Hesperidin [30]	Citrus		100 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ (IL-17, TNF-α, IL-1)
Osthole [31]	*Cnidium monnieri*		30 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ (IFN-γ, IL-17)
Baicalein [32]	*Scutellaria baicalensis*		100 mg/kg *i.p.*	C57BL/6 mice	Demyelination model	↓ (TNF-α, IL-1β)
Cannabidiol [33]	*Cannabis*		10 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ (IFN-γ, IL-17; PPAR-γ)
18β-Glycyrrhetinic acid [34]	*Glycyrrhiza inflata*		75 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ MAPK pathway
Astragaloside IV [36]	*Astragalus membranaceus*		20 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↑ glucocorticoid pathway

cells in the CNS. There are two major routes for NPs to exert anti-inflammation effects, by inhibiting inflammatory factors or by inhibiting microglia activation. The detailed mechanism is summarized in Table 2.

2.2.1. *Inhibiting inflammatory factors*

NPs have anti-inflammatory activity on MS mainly by inhibiting the inflammatory factor interleukin 1 and 17 (IL-1, IL-17), tumor necrosis factor alpha (TNF-α), Interferon gamma (INF-γ), which involves the mitogen-activated protein kinase (MAPK) pathway. By inhibiting the expression of these inflammatory factors, NPs reduce inflammation and relieve symptoms of MS.

2.2.1.1. Tripchlorolide. Tripchlorolide (purity 98%), a chemical extracted from the herb *Tripterygium wilfordii* Hook F, was injected intraperitoneally at the symptomatic stage to treat EAE mice. The results showed that at a dose of 40 mg/kg, tripchlorolide significantly decreased clinical score, inhibited relapse, reduced the severity of the disease and slowed down the development of EAE. In-depth research demonstrated that the mRNA and protein levels of T-bet, RAR-related orphan receptor gamma t (RoRγt), IFN-γ and IL-17 in the spinal cords were suppressed. Moreover, tripchlorolide restrained the expressions of ERK1/2-NF-κB and suppressed JAK/STAT signaling pathways [28].

2.2.1.2. Hesperidin. Hesperidin, a chemical existed in citrus species, has been proved with the ability to significantly reduce the clinical score of EAE mice by subcutaneous injection at dose of 100 mg/kg for seven consecutive days at the symptomatic stage of EAE. Further study found that EAE led to an increased level of IL-17 and pro-inflammatory cytokines, which could be reversed by hesperidin. EAE elevated TNF-α and IL-1, but the levels were significantly decreased after treatment with hesperidin, suggesting an anti-nerve inflammation role of hesperidin [29].

2.2.1.3. Osthole. Osthole is extracted from herb medicine *Cnidium monnieri* (L.) Cusson. After treated with 30 mg/kg of osthole (purity > 98%) by intraperitoneal at the symptomatic stage of EAE, the result of hematoxylin-eosin staining showed that osthole significantly reduced infiltration of inflammation to the white matter of the spinal cord and reduced the average inflammation score of EAE mice. ELISA analysis showed that IFN-γ and IL-17 level were significantly inhibited by osthole [30].

2.2.1.4. Baicalein. Baicalein, a chemical isolated from the roots of a Chinese medicinal herb *Scutellaria baicalensis*, is widely used as an anti-inflammatory remedy. To test the pharmacological activity of baicalein in the cuprizone exposed mice, baicalein was administered by intraperitoneal injection at a dose of 100 mg/kg at the symptomatic stage. The results showed that baicalein attenuated weight loss, motor dysfunction and cuprizone-induced demyelination. After exposure in cuprizone for 6 weeks, the increased mRNA expressions of the pro-inflammatory cytokines TNF-α and IL-1β, were attenuated by baicalein treatment [31].

2.2.1.5. Cannabidiol. Cannabidiol (purity > 99%) is a kind of non-addictive chemical extracted from medicinal plants *Cannabis*. After intraperitoneal injection of 10 mg/kg to mice at the symptomatic stage of EAE, spinal cord histological evaluation showed that cannabidiol significantly reduced the infiltration of inflammatory cells into the spinal cord. Coincidentally, the improvement of inflammation corresponds to lower clinical scores. After immune-histochemical analysis of the spinal cord slices, the results showed that cannabidiol reduced inflammatory factors INF-γ, IL-17 expression. Moreover, the level of peroxisome proliferator activated receptor-γ which reflected the anti-inflammatory strength *in vivo* was increased significantly after treatment [32].

2.2.2. *Inhibiting microglia activation*

Microglia, as phagocytic cells of the CNS, has dual functions to protect and support neurons within the CNS [35]. Microglia can rapidly response to MS and cause inflammatory cytokine secretion. It transferred to the lesion area, phagocytosed cellular debris and damaged neurons. Microglia plays a part in neuroprotection and growth promoting, on the other hand, it can generate inflammatory mediators, such as IL-1β, TNF-α and IL-6, which then accelerate MS injury [36–38].

2.2.2.1. 18β-Glycyrrhetinic acid. 18β-Glycyrrhetinic acid isolated from the traditional Chinese medicine *Glycyrrhiza inflata* (Fabaceae), has been used to treat EAE mice after intraperitoneally injection at a dose of 75 mg/kg at the pre-symptomatic stage of EAE. 18β-Glycyrrhetinic acid showed a significant inhibitory effect on the severity of EAE by reducing clinical scores, CNS inflammatory infiltration and demyelination compared with the vehicle control. 18β-Glycyrrhetinic acid inhibits microglia activation through suppression of MAPK signal pathway, which suppresses proinflammatory cytokine production and prevents the transfer of CD4+ T cells into the CNS [33].

2.2.2.2. Baicalein. After an intraperitoneal injection of 100 mg/kg to EAE mice at the symptomatic stage of cuprizone model mice, baicalein inhibited the increase in the number of microglia induced by cuprizone in the corpus callosum. Baicalein effectively inhibited the mRNA expression of microglial marker CD11b and astrocytic marker glial fibrillary acidic protein [31].

2.2.2.3. Astragaloside IV. Astragaloside IV, a chemical isolated from *Astragalus membranaceus* (Fisch.) Bge. After an intraperitoneal injection of astragaloside IV (purity > 98%) 20 mg/kg to mice before EAE induction, the limb defect of animals was remarkably alleviated. The average behavioral score and body weight loss of EAE mice were reduced, which indicated the preventive effect of astragaloside IV [39]. In addition, astragaloside IV can inhibit microglia activation both *in vivo* and *in vitro*. After treatment with astragaloside IV, the expression of proinflammatory factors IL-1β, TNF-α and iNOS were inhibited. Further research verified that astragaloside IV inhibited microglia activation *via* enhancing glucocorticoid receptor activity and facilitating glucocorticoid nuclear translocation [34].

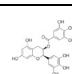
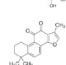
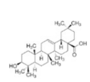
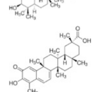
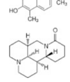
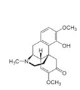
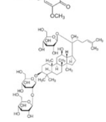
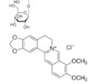
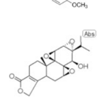
2.3. Effects on both the induction stage of autoimmune response and CNS inflammation

MS is initiated by self-reactive T cells that recognize antigens present in CNS, subsequently producing large numbers of pathogenic T cells which can lead to disease exacerbation by production of cytokines and induction of inflammation. During the disease progression, immunity and inflammation closely cooperate in the pathogenesis of MS. Firstly, autoimmune cells initiate diseases and produce inflammatory reactions, then inflammatory factor stimulates the immune cells, leading to immune disorders and inflammation aggravation. Therefore, in the treatment of MS, it is very meaningful to suppress inflammation and regulate immunity simultaneously. The mechanisms of NPs with effects on both the induction stage of autoimmune response and CNS inflammation were shown in Table 3.

2.3.1. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate, a kind of active chemical of green tea, has therapeutic effect on autoimmune diseases such as EAE. After administered orally with 0%, 0.15%, 0.3%, 0.6% epigallocatechin-3-gallate (purity > 95%) in diet before EAE induction, epigallocatechin-3-gallate delayed the onset of EAE, reduced the clinical score, and improved clinical symptoms, which indicated that epigallocatechin-3-gallate has good curative effect on EAE. In the aspect of anti-inflammation, epigallocatechin-3-gallate reduced infiltration of inflammatory cells in spinal cord of EAE mice and inhibited the production of INF-γ, IL-17, IL-1β and TNF-α, by which it could inhibit inflammatory reaction and reduce the occurrence of demyelination. Furthermore, epigallocatechin-3-gallate reduced the number of Th1 and Th17 cells while increased the number of Tregs in lymph nodes, the spleen, and the CNS following oral administration. Not only that, epigallocatechin-3-gallate inhibited the expression of transcription factor T-bet and RORγt, the specific transcription factor for Th1 and Th17 differentiation. Besides, the level of intercellular adhesion molecule 1 in plasma and the expression of CCR6 in CD4+ T cells were inhibited respectively. These results indicated that epigallocatechin-3-gallate might attenuate EAE autoimmune response by inhibiting immune cell infiltration and modulating the balance among pro- and anti-autoimmune CD4+ T cell subsets [40]. Another research suggested that epigallocatechin-3-gallate reduce the severity of the disease, decrease inflammatory and demyelinating lesion of the brain accompanied by reduced encephalitis T cell response and decreased expression of inflammatory cytokines and chemokines. The therapeutic effects of epigallocatechin-3-gallate were attributed to inhibition of the production of INF-γ and IL-17 in CD4+ T cells, down-regulation of STAT signaling pathway, decreased expression of T-bet and RORγt in encephalitogenic T cells as well as reduction co-stimulatory functions of antigen presenting cells as a result of altered expression of CD80 and CD86 [41].

Table 3
NPs with effects on both the induction stage of autoimmune response and CNS inflammation.

Compound name	Source	Structure	Dose	Animal strains	Model	Mechanism
Epigallocatechin-3-gallate [41,42]	Green tea		– *i.g.*	C57BL/6 mice	Chronic EAE	STAT pathway ↓ (IFN-γ, IL-17); ↓ T-bet, RORγ; ↓ (Th1, Th17);
Tanshinone IIA [43,44]	*Salvia miltiorrhiza*		25, 50 mg/kg, *i.p.*	Lewis rats; Sprague Dawley rat	Relapsing-remitting EAE	↓ CD4+, CD8+; ↓ IL-17, IL-23
Oleanolic acid [45]	*Olea europaea*		50 mg/kg *i.p.*	C57BL/J6 mice	Chronic EAE	↓ TNF-α, NF-κB, MCP-1, MCP-1α; ↑ IL-10
Celastrol [46]	*Tripterygium wilfordii*		1 mg/kg *i.p.*	Sprague Dawley rat	Relapsing-remitting EAE	↓ TNF-α, NF-κB; ↑IL-10; ↓ TLR, CD3+ lymphocytes
Matrine [47–50]	*Radix Sophorae Flave*		150, 200, 250 mg/kg *i.p.*	Wistar rat	Relapsing-remitting EAE	↑ Nrf2/HO-1 pathway; ↑ IL-4, IL-5, IL-10, TGF-1, Foxp3; ↓ CCL2, CXCL10; ↓ CCR2, CXCR3
Sinomenine [51]	*Sinomenium acutum*		50, 100, 200 mg/kg *i.p.*	Lewis rat	Acute EAE	↓ TNF-α, TNF-γ, RANTES, MIP-1, MIP-1α
Ginsenoside Rd [52]	*Pana notoginseng*		10, 20, 40, 80 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ IFN-γ, ↑ IL-4
Berberine [53,54]	*Coptis chinensis*		30, 200 mg/kg *i.g.*	C57BL/6 mice	Chronic EAE	JAK/STAT pathway ↓ (p-Tyk2, p-JAK1/2, p-STAT1, p-STAT4, p-STAT3); NF-κB pathway
Triptolide [55]	*Tripterygim wilfordii*		100 μg/kg *i.g.*	C57BL/6 mice	Chronic EAE	NF-κB pathway ↑ (IκBα)

2.3.2. Tanshinone IIA

To study the potential therapeutic effect of tanshinone IIA on EAE rats, EAE rats were administered with tanshinone IIA and placebo intraperitoneally at the pre-symptomatic stage. Compared with the placebo group, tanshinone IIA treatment significantly improved clinical symptoms and pathological changes, including CNS inflammatory cells infiltration, demyelination and reduction in CD4+ T cells, CD8+ T cells and macrophages/microphage populations. In addition, tanshinone IIA also lowered the brain and serum level of IL-17 and IL-23 in EAE rats and inhibited the occurrence of nerve inflammation [42].

2.3.3. Oleanolic acid

Oleanolic acid is a chemical that exists widely in the fruit of *Olea europaea*. EAE mice treated with 50 mg/kg oleanolic acid (purity > 98%) by intraperitoneal injection at the pre-symptomatic stage showed a delayed first onset time, improved clinical symptoms and reduced clinical score of EAE. Oleanolic acid reduced leukocyte adhesion and aggregation in the cerebral microcirculation caused by EAE and reduced the infiltration of inflammatory cells in the CNS. In addition, oleanolic acid inhibited the expression of Th1 cytokines TNF-α, IFN-γ and chemokines MCP-1, MCP-1α by regulating Th1/Th2 polarization, whereas Th2 cytokine IL-10 expression increased significantly [44].

2.3.4. Celastrol

Celastrol was isolated from the root and bark of traditional medicinal *Tripterygium wilfordii* Hook. After administrated to EAE mice at the symptomatic stage, celastrol (purity > 98%) caused a reduction in the clinical score and inhibition on the recurrence of the disease. The levels of TNF-α, NF-κB in serum, nitrite in brain and spinal cord were reduced, and the content of anti-inflammatory factor IL-10 was significantly increased. Further studies showed that clinical scores positively correlated with the content of TNF-α, NF-κB and nitrite, and negatively correlated with CD3+ T lymphocyte number in brain tissue and the level of IL-10 in serum. Toll like receptor (TLR) overexpression is considered as promoting the inflammatory process, increasing the production of Th1 cytokines, leading to axonal demyelination. Histopathological results showed that celastrol could decrease the number of CD3+ T lymphocytes, and the level of Toll like receptor, playing an important role in treatment of EAE [45].

2.3.5. Matrine

Matrine is a quinolizidine alkaloid chemical extracted from medicinal herb *Radix Sophorae Flave*. Following intraperitoneal injection of matrine to rats at the pre-symptomatic stage of EAE, the clinical score and the initial weight loss rate decreased significantly as well as the progression of the disease was slowed down. Hematoxylin-eosin staining of the sections of spinal cord demonstrated that inflammatory cell infiltration was regulated down remarkably compared with the control group. Matrine significantly increased serum levels of Th2 type cytokine IL-4, IL-5, IL-10 and TGF-1 of Tregs, and increased the expression of Tregs transcription factor Foxp3 [46]. In EAE mice, the level of CCL2 and CXCL10 were significantly upregulated. After administered at the pre-symptomatic stage, matrine attenuated severity of EAE by acting on CCR2 and CXCR3 receptor, reducing the CCL2 and CXCL10 levels in the periphery and the CNS [48]. What's more, nuclear factor erytheroid-derived-2-like 2 (Nrf2) and heme oxygenase 1 (HO-1) also play a crucial role in the inhibition of oxidation and inflammatory, and matrine significantly increases the base level of them. The above results indicated that matrine have both effects of anti-inflammation and immune regulation in the treatment of the demyelinating disease [46].

2.3.6. Sinomenine

Sinomenine extracted and purified from traditional Chinese medicine *Sinomenium acutum*. After administered intraperitoneally at a dose of 50, 100, 200 mg/kg at the pre-symptomatic stage, sinomenine (purity > 95%) showed a dose related effect on decreasing clinical score and the initial weight loss rate, improving the clinical symptoms and delaying the ongoing of EAE after treatment. A decreased expression of TNF-α and IFN-γ in the spinal cord after sinomenine treatment showed anti-inflammatory effect. With the decrease of TNF-α and IFN-γ expression level, the inflammatory cells infiltration into the spinal cord was alleviated according to the histopathology results, and the mRNA level of regulated upon activation, normal T cell expressed and secreted factor (RANTES), MIP-1α and MCP-1 was inhibited in EAE mice. In addition, sinomenine reduced the proliferation of T cells after treatment with EAE inducer myelin basic protein ($MBP_{68–82}$) *in vitro* [50].

2.3.7. Ginsenoside Rd

Ginsenoside Rd (purity > 98%) extracted from the traditional Chinese medicine *Pana notoginseng* was administered by intraperitoneal injection at doses of 10, 20, 40, 80 mg/kg to treat EAE mice at the pre-symptomatic stage. The results illustrated that ginsenoside Rd alleviated the symptoms, reduced the clinical score and inflammatory scores of the disease significantly as well as inhibited the demyelination in lumbar spinal cords of EAE mice. According to the histopathological results, it is reasonable to deduce that the infiltration of inflammatory cells such as macrophages, T lymphocytes and B lymphocytes has been reduced. *In vivo* and *in vitro* experiment showed that ginsenoside Rd reversed the adverse immune responses induced by EAE, which include inhibition of IFN-γ production, enhancement of IL-4 level, decrease of the ratio of IFN-γ/IL-4, maintaining of the balance of Th1/Th2 and promotion of the Th2 shift [51].

2.3.8. Berberine

Berberine, an oquinoline alkaloid derivative, has extensive pharmacological activities. After gavaged with 30 mg/kg berberine (purity > 95%) to EAE mice at the symptomatic stage, both the clinical score and the severity of the disease have been reduced. Further neuropathological analysis revealed that compared with the control group, berberine inhibited production of Th1 and Th17 cytokines and decreased the number of inflammatory cells infiltrating into the white matter of the CNS, resulting in an excellent anti-inflammatory activity. Berberine has effects on Th1 and Th17 cell differentiation by adjusting the JAK/STAT pathway, but it has no effect on CD4+ Foxp3 Tregs, retaining the normal function of other immune cells. Berberine regulated function of Th1/Th2 by affecting the expression and function of costimulatory molecules and the production of IL-6, which was recognized as crucial factor of inhibition of NF-κB activity in CD11+ antigen presenting cells [52].

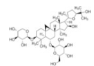
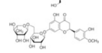
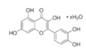
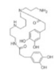
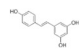
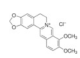
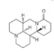
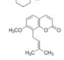
2.3.9. Triptolide

Triptolide is a chemical mainly isolated from Chinese herb *Tripterygium wilfordii* Hook F. Triptolide significantly delayed the autoimmune demyelination onset of EAE mice and reduced the severity of the disease. Meanwhile, levels of inflammation and demyelination in the CNS were improved by triptolide. In the aspect of anti-inflammatory, triptolide could inhibit the mRNA expression of cytokines IFN-γ, TNF-α, IL-12, IL-6, IL-23 and IL-17 in monocytes in the spleen and spinal cord. Triptolide has inhibition effect on NF-κB DNA binding activity by attenuating phosphorylation and inhibiting degradation of cytoplasmic inhibitors IκBα. Furthermore, another research indicated that triptolide suppressed inflammation and demyelination *via* inhibiting IκBα phosphorylation and NF-κB nuclear translocation by stabilization of NF-κB/IκBα complex. In immunoregulation, the expression of Foxp3 was up-regulated by treatment of triptolide, suggesting the induction of Tregs in EAE mice after treating with triptolide [54].

3. Nervous system protection

Oxidative stress plays an important role on neuronal damage in the pathogenesis of MS [55]. In EAE lesion, macrophages and microglia produce reactive oxygen species (ROS) and reactive nitrogen species

Table 4
NPs with nervous system protection effect.

Compound name	Source	Structure	Dose	Animal strains	Model	Mechanism
Astragaloside IV [35]	*Astragalus membranaceu*		20 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ ROS, iNOS, p53; ↑ SOD GPx
Hesperidin [30]	Citrus		100 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↓ TBARS; ↑ GSH, CAT, GPx, SOD
Quercetin [64]	*Quercus iberica*		50 mg/kg *i.g.*	Wistar rat	Experimental demyelination	↑ AchE; ↓ MDA
Kukoamine B [65]	*Cortex lyciiradices*		–	–		↓ MAPK pathway; ↑ PI3K-AKT pathway; ↑ SOD, CAT, GPx; ↓ MDA, ROS
Resveratrol [66,67]	Nuts, berries, grapes		10, 20, 50 mg/kg, 250 mg/kg *i.p.*, *i.g.*	C57BL/L6 mice	Chronic EAE; Experimental demyelination	↓ NOX2, NOX4, NADPH, TBARS; ↑ GSH, SOD
Berberine [53]	*Coptis chinensis*		30 mg/kg *i.g.*	C57BL/6 mice	Chronic EAE	↓ MMP-9
Matrine [50]	*Radix Sophorae Flave*		200 mg/kg *i.p.*	Wistar rat	Relapsing-remitting EAE	↓ Aβ, BACE-1
Osthole [31]	*Cnidium*		30 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↑ BDNF

(RNS) which are associated with inflammation [56]. In addition, ROS and RNS can cause DNA strand broken and accumulation of oxidized phospholipids in cytoplasm [57]. NPs exert its neuroprotective function through anti-oxidative stress, anti-neuronal apoptosis, and anti-demyelination. Many NPs have effects of antioxidant, and promote the production of antioxidant enzymes, which decrease intracellular levels of ROS and RNS, and attenuate symptoms of EAE finally. Malondialdehyde (MDA) is a degradation product of lipid peroxidation which reflecting lipid peroxidation [58]. The activity of acetylcholine ester can respond to a variety of injuries, including oxidative stress [59]. β amyloid (Aβ) production is controlled by b-site amyloid precursor protein cleaving enzyme (BACE-1), which can promote Aβ generation, and induce astrocyte activation, synaptic integrity damage and neuronal death [60,61]. There is evidence that MMP-9 is associated with MS. Up-regulation of the expression of MMP-9 will increase the permeability of the BBB, which promote leukocytes infiltrating into the CNS, and leading to demyelination [62]. The detailed mechanism is summarized in Table 4.

3.1. Astragaloside IV

After treatment of EAE mice with astragaloside IV, there is an inhibition effect on expression of ROS and proinflammatory cytokines, with increased activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx), decreased activity of iNOS, p53 and phosphorylated tau protein, as well as an increased Bcl-2/Bax ratio. In neuroblastoma SH-SY5Y cells, astragaloside IV reduced the level of reactive oxygen species and phosphorylated protein. In BV-2 cells, astragaloside IV can inhibit IFN-γ stimulation, promote iNOS levels and reduce the damage of nerve cells [16].

3.2. Hesperidin

The lipid peroxidation in EAE mice caused an increased thiobarbituric acid reactive substances (TBARS) level, and a decreased level of antioxidant factor, including glutathione (GSH), catalase (CAT), GPx, and SOD. To test the pharmacological activity of hesperidin in EAE mice, EAE mice were treated with hesperidin, and the results showed that hesperidin could inhibit the growth of TBARS, as well as the increased level of GSH, CAT, GPx, and SOD. Hesperidin prevents the oxidative stress of EAE because it can increase antioxidant factor to reduce lipid peroxidation in brain tissue, achieving a protective effect on CNS [11].

3.3. Quercetin

Quercetin, a chemical which existing in a variety of fruits and vegetables, has good antioxidant ability. After gavaged at 50 mg/kg dose to ethidium bromide model rats at the pre-symptomatic stage, quercetin significantly reduced the mistakes of beam walking test and foot fault test as well as promoted recovery of motor function of experimental demyelination mice, suggesting protecting effects on demyelinating diseases. Further determination of biochemical indicators found that quercetin prevented the decrease of acetylcholinesterase activity indicating that quercetin protected cholinergic neurotransmission. Moreover, quercetin prevented the increase of MDA levels in EAE rats. The antioxidant activity of quercetin is outstanding, and thus results in prominent neuroprotective effect [63].

3.4. Kukoamine B

Kukoamine B (purity > 95%) is the main active chemical of traditional Chinese medicine *Cortex lyciiradices*. Inhibition test of oxidative stress in SH-SY5Y cells indicated that the kukoamine B treatment significantly improved the cell viability and recovery of mitochondrial membrane potential. Furthermore, kukoamine B enhanced activity of antioxidant enzymes SOD, CAT and GPx, and decreased the content of MDA. Moreover, kukoamine B inhibited the formation of ROS and the mitochondrial apoptotic pathway of MAPKs (p38, JNK, ERK), but actived the PI3K-AKT pathway. These results showed that kukoamine B exerted a neuroprotective effect by inhibiting oxidative stress in cells [64].

3.5. Resveratrol

Resveratrol, a non-flavonoid polyphenol compound, has effects of antioxidant, anti-inflammatory, antiviral and antitumor. Resveratrol was administrated by intraperitoneal injection (10, 25, 50 mg/kg) to EAE mice at the pre-symptomatic stage, the results showed that the resveratrol treatment reduced the clinical score, the average clinical score, and maximum clinical score. The NOX isoforms were involved in production of ROS in a variety of cells after stimulation by various growth factors or cytokines. Additionally, resveratrol significantly inhibited expression of iNOS and IL-1. It increased the expression of transcription enzyme of anti-inflammatory cytokine IL-10 in brain, and the activity of NADPH has been inhibited by downregulating the expression of NADPH oxidase NOX2 and NOX4 [65]. In addition, resveratrol treatment significantly diminished TBARS and increased both GSH level and SOD activity [66].

3.6. Berberine

Laminin involved in neuronal development, survival and regeneration, and is the main component of the extracellular matrix. Matrix metalloproteinase-9 (MMP-9) damages the laminin surrounding nerve cells, which plays an important role in neuronal apoptosis. Berberine inhibited the activity of MMP-9 and reduced the degradation of laminin, thereby protecting neurons from damage caused by autoimmune demyelination [52].

3.7. Matrine

Matrine reduced the level of myelin basic protein in CNS, and inhibited Aβ and BACE-1 expression, which was conducive to the expression of brain derived neurotrophic factor that would promote neuronal survival and neurite growth. It indicated that matrine protected axons from inflammation damage of the CNS effectively [49].

3.8. Osthole

H_2O_2 decreased the cell survival rate significantly, but osthole reduced the cytotoxic effect, which indicated that osthole had protection effects in a disadvantageous environment. In addition, osthole could promote the generation of brain derived neurotrophic factor (BDNF) and maintain cell survival [30].

4. Nervous system repairing

Regeneration plays an important role in maintaining the normal equilibrium of the CNS as well as in promoting its repair upon demyelination. Several lines of evidence indicate that regeneration usually occurs by promoting the secretion of neurotrophins (NGF, BDNF) which can promote oligodendrocyte precursor cell proliferation and repair of the nervous system [67–69]. NPs can act on oligodendrocyte precursor cells directly and promote oligodendrocyte precursor cells differentiate into oligodendrocytes. Besides, by acting on neural stem cells, NPs increase the survival rate of neural stem cells and promote the differentiation of neural stem cells into oligodendrocytes, which promotes the formation of myelin sheath, then contributing to remyelination. The mechanisms of NPs with effects of nervous system repairing were shown in Table 5.

4.1. 18β-Glycyrrhetinic acid

18β-Glycyrrhetinic acid treatment of EAE mice promoted remyelination in the CNS. 18β-Glycyrrhetinic acid can inhibit inflammation-induced blockade of brain-derived neurotrophic factor expression in microglia, which will promote remyelination in the CNS of EAE mice [33].

4.2. Scutellarin

Scutellarin is a kind of flavonoids from traditional Chinese medicine *Erigeron breviscapus* Hand-Mazz and has functions of protecting neurons and promoting the formation of nerve. After treatment with scutellarin (purity 98.6%) at the pre-symptomatic stage, the motor function of cuprizone model mice was improved, demyelination of the corpus callosum was reduced and the apoptosis of neural stem cells was reduced. Scutellarin can increase the survival rate of neural stem cells and promote the differentiation of neural stem cells into oligodendrocytes. It reduces the differentiation of neural stem cells into astrocytes and promotes the maturation of oligodendrocytes to form a myelin sheath, serving as a therapeutic agent for remyelination [70].

4.3. Cannabidiol

MS induced a reduced BDNF expression, while cannabidiol could enhance BDNF levels in the CNS, which is beneficial for neuronal function and remyelination [32].

4.4. Matrine

Matrine promoted oligodendrocyte precursor cells proliferation and increased the oligodendrocyte numbers, which indicated that matrine treatment could promote oligodendrocyte precursor cells maturation into oligodendrocytes for myelin repair in EAE [49].

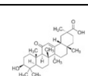
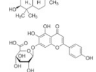
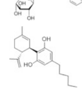
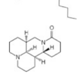
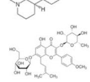
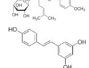
4.5. Icariin

Mice were fed with cuprizone to induce acute demyelination and oligodendrocytes degeneration. Remarkably, icariin prevented amount of mature oligodendrocytes loss as well as promoted remyelination and regeneration of axons, which might be attributed to improving the expression of NGF [71].

4.6. Resveratrol

Resveratrol has a good effect on cuprizone model mice, the results of brain tissue staining suggest that cuprizone caused severe

Table 5
NPs with nervous system repairing effect.

Compound name	Source	Structure	Dose	Animal strains	Model	Mechanism
18β-Glycyrrhetinic acid [34]	*Glycyrrhiza inflata*		75 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↑ NGF, BDNF
Scutellarin [71]	*Scutellaria barbata*		50 mg/kg *i.p.*	C57BL/6 mice	Experimental demyelination	↑ Neural stem cells, oligodendrocytes; ↓ MAPK pathway
Cannabidiol [33]	*Cannabis*		10 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↑ BDNF
Matrine [50]	*Radix Sophorae Flave*		200 mg/kg *i.p.*	C57BL/6 mice	Chronic EAE	↑ OPC, oligodendrocytes
Icariin [23]	*Herba epimedii*		25 mg/kg *i.g.*	C57BL/6 mice	Chronic EAE	↑ NGF
Resveratrol [67]	Nuts, berries, grapes		250 mg/kg *i.g.*	C57BL/L6 mice	Experimental demyelination	↑ MBP, Olig1

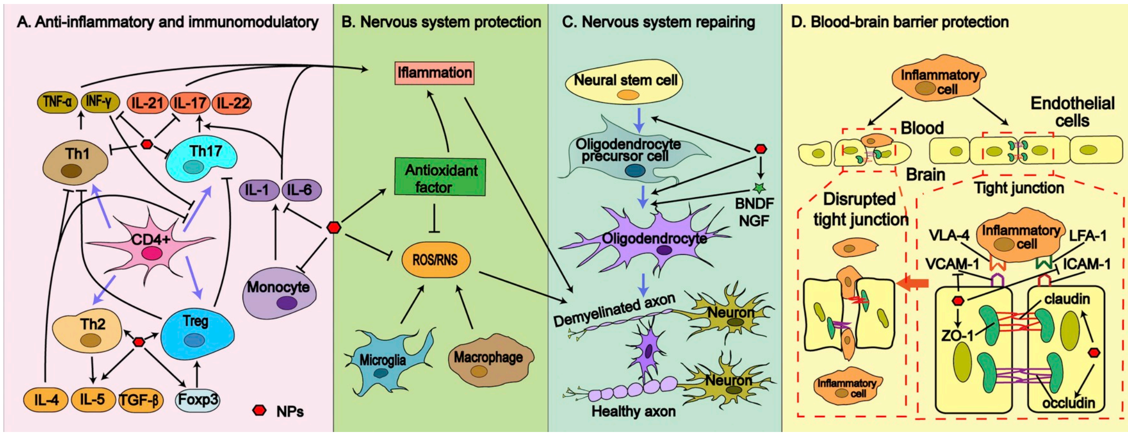


Fig. 1. Mechanisms of NPs in the treatment of MS. A. Anti-inflammatory and immunomodulatory effects of NPs. B. Nervous system protection. C. Nervous system repairing. D. BBB protection.

demyelination, while resveratrol promoted myelin regeneration [66]. Oligodendrocyte transcription factor-1 (Olig1) is an important endogenous transcription factor which is expressed in oligodendrocyte precursor cells and closely related to repairing demyelinating injury in EAE model [72]. Resveratrol could antagonize the decrease of MBP and Olig1 induced by cuprizone, and enhance the expression of Olig1 and MBP.

5. BBB protection

MS causes BBB dysfunction and damages integrity of BBB, then recruits many inflammatory cells infiltrating into the CNS, eventually leading to demyelination [73]. There are two major factors leading to pathological BBB breakdown: the paracellular leakage of inflammatory mediators into the CNS *via* the disrupted tight junctions and the transcellular entry of inflammatory cells across brain microvascular endothelial cells *via* the upregulation of adhesion molecules [74]. Claudin-5 is one of the key proteins of tight junction, and the decrease of its level will enhanced BBB permeability [75,76]. The VCAM-1 and IVAM-1 consisted in brain microvascular endothelial cells are essential adhesion molecules, which plays a central role in the recruitment of inflammatory cells across the BBB *via* binding to their respective counter receptors leukocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) existed in the leukocytes [77–80]. The levels of tight junction proteins, such as adhesion molecules (ZO-1), occludin, ICAM-1 and VCAM-1 were detected by western blot. It was found that resveratrol inhibited loss of ZO-1, occludin and claudin-5 induced by EAE, and repressed adhesion molecule ICAM-1 and VCAM-1 [65]. It indicates that resveratrol has an ability to protect BBB integrity of the EAE mice. Tanshinone II A protected BBB by increasing the expression of the tight junction protein ZO-1, claudin 5 and occluding of endothelial cell. In addition, tanshinone II A inhibited the expression of adhesion molecules ICAM-1 and VCAM-1 and chemokines CCL3, CCL5 and CX3C-chemokine receptor 1, which is the crucial factors for immune cell adhesion and across the BBB. Hence, tanshinone II A prevented the infiltration of immune cells into CNS by strengthening the integrity of BBB [43]. In addition, astragaloside IV, oleanolic acid, ginsenoside Rd and berberine also protect the BBB, reduce permeability, achieving a therapeutic effect [39,44,51,52].

6. Discussion

According to the current research results, NPs are very effective and have great potential in the treatment of MS. Moreover, there are multiple mechanisms of NPs in treatment of MS, urgently needing to be better understood. At present, we can perceive from the references that the general mechanisms of NPs for EAE therapy are anti-inflammatory, immune regulation, neuroprotection, nervous system repairing and BBB protection (Fig. 1). Some NPs have both anti-inflammatory and immune regulation properties. Some even have multiple functions, plus neuroprotection and nervous system repairing simultaneously. For anti-inflammatory, the main mechanism is to reduce the level of inflammatory factors. Pro-inflammatory factors like TNF-α, IL-1β usually activate immune cells involved in the immune response, which will cause tissue damage seriously [81]. So anti-inflammatory activity is important for treatment of MS *via* preventing CNS from continuous injury. NPs can inhibit inflammatory cells infiltrating to CNS and suppress microglia activation, which can avoid sustained damage to the CNS. Due to inflammation of the CNS is usually caused by an abnormal immune response, immune regulation is also important to MS treatment. The mechanism of immunoregulation is maintaining Th1/Th2 balance, inhibition of Th17 involved in inflammatory response, promoting Tregs immunoregulatory function, and regulation of monocyte and macrophage. Generally, inflammation is often triggered by abnormal immune response and cause the disease to deteriorate. So, we should treat MS by correcting abnormal immune response and regulating immune cell activity at the same time, to achieve desired therapeutic effect. Sinomenine has been reported to be effective in the treatment of EAE mice *via* anti-inflammatory and immune regulation effect [50]. In addition, as the good effect of anti-inflammatory and immune regulation, sinomenine has been widely used in the treatment of rheumatoid arthritis in clinic [82]. Immune regulation activity of NPs is not only effective *in vitro*, but also remarkably effective *in vivo*. Although the immune response in MS is very complex, the effects of NPs are satisfactory. However, this benign result can't only attribute to immunoregulatory. BBB is disrupted in the EAE model, which is associated with the loss of tight junction proteins [83]. Furthermore, the clinical severity associated with the degree of BBB disruption has been demonstrated [84]. While reducing inflammation and correcting abnormal immune responses, NPs can also prevent tight junction protein loss, protect the BBB and reduce the infiltration of inflammatory cells in CNS. When the nervous system is damaged, NPs can play a protective role. In the case of neuronal damage, oxidative stress plays a major role, so it is very important to protect the nervous system from oxidant stress, and inhibit level of MMP-9 and Aβ that can lead to neuronal apoptosis [85–87]. In general, myelination damage caused by MS is irreversible, because remyelination is blocked by many factors. There are two kinds of factors widely accepted, non-disease related factors and disease-specific factors. Disease-specific factors include deficiency of precursor cells, failure of precursor cell recruitment, or failure of precursor cell differentiation and maturation [88]. The currently available medications can control inflammation and correct abnormal immune responses, but the injured myelin sheath was not repaired effectively. The result of traditional treatment is that the disease progression has been halted

Table 6
The mechanisms that different NPs involved in the treatment of MS.

Compound name	Anti-inflammatory	Immunomodulatory	Nervous system protection	Nervous system repairing	Blood-brain barrier protection
Tripchlorolide	+				
Hesperidin	+		+		
Osthole	+		+		
Baicalein	+				
Cannabidiol	+			+	
18β-Glycyrrhetinic acid	+			+	
Astragaloside IV	+		+		+
Icariin		+		+	
Plumbagin		+			
Apigenin		+			
Salvianolic acid B		+			
Eriocalyxin B		+			
Epigallocatechin-3-gallate	+	+			
Tanshinone IIA	+	+			+
Oleanolic acid	+	+			+
Celastrol	+	+			
Matrine	+	+	+	+	
Sinomenine	+	+			
Ginsenoside Rd	+	+			+
Berberine	+	+	+		+
Triptolide	+	+			
Quercetin			+		
Kukoamine B			+		
Resveratrol			+	+	
Scutellarin				+	

temporarily, but the nervous system damage will lead to motor dysfunction permanently.

Hence for MS patients, the nervous system repair is particularly important. Considering that the currently available medications for multiple sclerosis do not directly promote repair [89], new medicines are urgently needed to be developed to treat MS. Therefore, many researches have attempted to achieve better therapeutic effects through remyelination. The repair mechanism of NPs is to promote oligodendrocyte precursor cells maturation and differentiate into oligodendrocytes by the stimulation of BDNF and NGF, and achieve the goal of myelination regeneration finally. NPs can also promote the differentiation of neural stem cells to achieve myelination [90–92]. According to the references, the current drug with function of remyelinating is still rare, but this pharmacological activity for MS is vital. Fortunately, we have found many NPs have the activity of promoting nerve system repair *in vitro*, and the results of promoting myelin regeneration *in vivo* are more convincing. After treatment with 18β-glycyrrhetinic acid, the expression of MBP and proteolipid protein was increased in EAE mice, the number of myelinated axons and newly formed myelinated axons were increased, and the proliferation of oligodendrocyte precursor cells was promoted [33]. Icariin prevented amount of mature oligodendrocytes loss as well as promoted remyelination and regeneration of axons [71]. Resveratrol reversed cuprizone-induced demyelination and promoted myelin proteins gene expression and myelin regeneration [66]. In summary, NPs treatment of MS have characteristic of multi-pathway, multi-target, and synergistic effect of various mechanisms to work together to play a therapeutic role (Table 6).

7. Conclusions

MS causes irreversible myelin damage, which can't be completely cured by the current medicines on the market. While NPs have showed excellent curative effect on MS in aspects of anti-inflammation, immune regulation, nervous system protection, nervous system repairing, and BBB protection. At present, some NPs have already been used in clinical for the treatment of autoimmune diseases, such as sinomenine for the treatment of rheumatoid arthritis [82]. We conclude that the application of NPs has great potential to improve MS therapy in the future, and it is of great value to further develop and in-depth study the potential therapeutic effect of NPs on MS.

Abbreviations

MS	multiple sclerosis
CNS	central nervous system
BBB	blood-brain barrier
PPMS	primary-progression MS
NPs	natural products
IL	interleukin
TNF-α	tumor necrosis factor alpha
INF-γ	interferon gamma
MAPK	mitogen-activated protein kinase
EAE	experimental autoimmune encephalomyelitis
RoRγt	RAR-related orphan receptor gamma t
Th	T helper cell
Tregs	regulatory T cells
CXCL10	CXC chemokine ligand-10
TLR	Toll like receptor
CCL2	chemokines chemokine ligand-2
MCP-1	monocyte chemoattractant protein 1
Nrf2	nuclear factor erythroid-derived-2-like 2
HO-1	heme oxygenase 1
RANTES	normal T cell expressed and secreted factor
MBP	myelin basic protein
ROS	reactive oxygen species
RNS	reactive nitrogen species
MDA	malondialdehyde
Aβ	β amyloid
BACE-1	B-site amyloid precursor protein cleaving enzyme
MMP-9	matrix metalloproteinase-9
SOD	superoxide dismutase
GPx	glutathione peroxidase
TBARS	thiobarbituric acid reactive substances
GSH	glutathione
CAT	catalase
BDNF	brain derived neurotrophic factor
Olig1	oligodendrocyte transcription factor-1

LFA-1 leukocyte function-associated antigen-1
VLA-4 very late antigen-4

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by National Natural Science Foundation of China (81202924, 81773909, 81703711), Shanghai Rising-Star Program of China (13QA1403400), Shanghai talent development funds (201665), Excellent Medical Profession Scholarship of Shanghai municipal commission of health and family planning (2017YQ060), Fudan University & The Open Project Program of Key Lab of Smart Drug Delivery, Fudan University (SDD2017-01), Ministry of Education of China.

References

[1] A. Nylander, D.A. Hafler, Multiple sclerosis, J. Clin. Invest. 122 (4) (2012) 1180–1188.
[2] L. Steinman, Immunology of relapse and remission in multiple sclerosis, Annu. Rev. Immunol. 32 (2014) 257–281.
[3] M.A. Friese, B. Schattling, L. Fugger, Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis, Nat. Rev. Neurol. 10 (4) (2014) 225–238.
[4] D.H. Mahad, B.D. Trapp, H. Lassmann, Pathological mechanisms in progressive multiple sclerosis, Lancet Neurol. 14 (2) (2015) 183–193.
[5] R. Brandstadter, S.I. Katz, The use of natalizumab for multiple sclerosis, Neuropsychiatr. Dis. Treat. 13 (2017) 1691–1702.
[6] C. Guarnera, P. Bramanti, E. Mazzon, Comparison of efficacy and safety of oral agents for the treatment of relapsing-remitting multiple sclerosis, Drug Des. Devel. Ther. 11 (2017) 2193–2207.
[7] N. Bergvall, C. Makin, R. Lahoz, N. Agashivala, A. Pradhan, G. Capkun, A. Petrilla, S.U. Karkare, M.C. Balderston, J.R. Korn, Comparative effectiveness of fingolimod versus interferons or glatiramer acetate for relapse rates in multiple sclerosis: a retrospective US claims database analysis, Curr. Med. Res. Opin. 29 (2013) 1647–1656.
[8] D.S. Reich, C.F. Lucchinetti, P.A. Calabresi, Multiple sclerosis, N. Engl. J. Med. 378 (2018) 169–180.
[9] K.M. Danikowski, S. Jayaraman, B.S. Prabhakar, Regulatory T cells in multiple sclerosis and myasthenia gravis, J. Neuroinflammation 14 (1) (2017) 117.
[10] C.A. Dendrou, L. Fugger, M.A. Friese, Immunopathology of multiple sclerosis, Nat. Rev. Immunol. 15 (2015) 545–558.
[11] D.O. Gor, N.R. Rose, N.S. Greenspan, TH1-TH2: a procrustean paradigm, Nat. Immunol. 4 (6) (2003) 503–505.
[12] M. Kostic, I. Stojanovic, G. Marjanovic, N. Zivkovic, A. Cvetanovic, Deleterious versus protective autoimmunity in multiple sclerosis, Cell. Immunol. 296 (2) (2015) 122–132.
[13] I. Raphael, S. Nalawade, T.N. Eagar, T.G. Forsthuber, T cell subsets and their signature cytokines in autoimmune and inflammatory diseases, Cytokine 74 (1) (2015) 5–17.
[14] T. Kuwabara, F. Ishikawa, M. Kondo, T. Kakiuchi, The role of IL-17 and related cytokines in inflammatory autoimmune diseases, Mediat. Inflamm. 2017 (2017) 3908061.
[15] A. Jones, D. Hawiger, Peripherally induced regulatory T cells: recruited protectors of the central nervous system against autoimmune neuroinflammation, Front. Immunol. 8 (2017) 532.
[16] K. Ko, S. Yamazaki, K. Nakamura, et al., Treatment of advanced tumors with agonistic anti-GITR mAb and its effects on tumor-infiltrating Foxp3+CD25+CD4+ regulatory T cells, J. Exp. Med. 202 (7) (2005) 885–891.
[17] B.J. Biller, R.E. Elmslie, R.C. Burnett, A.C. Avery, S.W. Dow, Use of FoxP3 expression to identify regulatory T cells in healthy dogs and dogs with cancer, Vet. Immunol. Immunopathol. 116 (1–2) (2007) 69–78.
[18] M. Abdolahi, P. Yavari, N.M. Honarvar, S. Bitarafan, M. Mahmoudi, A.A. Saboor-Yaraghi, Molecular mechanisms of the action of vitamin a in Th17/Treg axis in multiple sclerosis, J. Mol. Neurosci. 57 (4) (2015) 605–613.
[19] I.F. Charo, R.M. Ransohoff, The many roles of chemokines and chemokine receptors in inflammation, N. Engl. J. Med. 354 (6) (2006) 610–621.
[20] E.E. Ubogu, M.B. Cossoy, R.M. Ransohoff, The expression and function of chemokines involved in CNS inflammation, Trends Pharmacol. Sci. 27 (1) (2006) 48–55.
[21] A. Szczuciński, J. Losy, Chemokines and chemokine receptors in multiple sclerosis. Potential targets for new therapies, Acta Neurol. Scand. 115 (3) (2007) 137–146.
[22] R. Shen, W. Deng, C. Li, G. Zeng, A natural flavonoid glucoside icariin inhibits Th1 and Th17 cell differentiation and ameliorates experimental autoimmune encephalomyelitis, Int. Immunopharmacol. 24 (2) (2015) 224–231.
[23] K. Zhang, Z. Ge, Y. Da, et al., Plumbagin suppresses dendritic cell functions and alleviates experimental autoimmune encephalomyelitis, J. Neuroimmunol. 273 (1–2) (2014) 42–52.
[24] R. Ginwala, E. McTish, C. Raman, et al., Apigenin, a natural flavonoid, attenuates EAE severity through the modulation of dendritic cell and other immune cell functions, J. NeuroImmune Pharmacol. 11 (1) (2016) 36–47.
[25] Z. Dong, D. Ma, Y. Gong, T. Yu, G. Yao, Salvianolic acid B ameliorates CNS autoimmunity by suppressing Th1 responses, Neurosci. Lett. 619 (2016) 92–99.
[26] Y. Lu, B. Chen, J.H. Song, et al., Eriocalyxin B ameliorates experimental autoimmune encephalomyelitis by suppressing Th1 and Th17 cells, Proc. Natl. Acad. Sci. U. S. A. 110 (6) (2013) 2258–2263.
[27] I. Selmaj, M.P. Mycko, C.S. Raine, K.W. Selmaj, The role of exosomes in CNS inflammation and their involvement in multiple sclerosis, J. Neuroimmunol. 306 (2017) 1–10.
[28] J. Zhang, Y.Q. Zeng, J. Zhang, et al., Tripchlorolide ameliorates experimental autoimmune encephalomyelitis by down-regulating ERK1/2-NF-κB and JAK/STAT signaling pathways, J. Neurochem. 133 (1) (2015) 104–112.
[29] O. Ciftci, C. Ozcan, O. Kamisli, A. Cetin, N. Basak, B. Aytac, Hesperidin, a citrus flavonoid, has the ameliorative effects against experimental autoimmune encephalomyelitis (EAE) in a C57BL/J6 mouse model, Neurochem. Res. 40 (6) (2015) 1111–1120.
[30] Z. Gao, Q. Wen, Y. Xia, et al., Osthole augments therapeutic efficiency of neural stem cells-based therapy in experimental autoimmune encephalomyelitis, J. Pharmacol. Sci. 124 (1) (2014) 54–65.
[31] M. Hashimoto, S. Yamamoto, K. Iwasa, et al., The flavonoid Baicalein attenuates cuprizone-induced demyelination via suppression of neuroinflammation, Brain Res. Bull. 135 (2017) 47–52.
[32] S. Giacoppo, F. Pollastro, G. Grassi, P. Bramanti, E. Mazzon, Target regulation of PI3K/Akt/mTOR pathway by cannabidiol in treatment of experimental multiple sclerosis, Fitoterapia 116 (2017) 77–84.
[33] J. Zhou, W. Cai, M. Jin, et al., 18β-Glycyrrhetinic acid suppresses experimental autoimmune encephalomyelitis through inhibition of microglia activation and promotion of remyelination, Sci. Rep. 5 (2015) 13713.
[34] H.S. Liu, H.L. Shi, F. Huang, et al., Astragaloside IV inhibits microglia activation via glucocorticoid receptor mediated signaling pathway, Sci. Rep. 6 (2016) 19137.
[35] W.J. Streit, Microglia as neuroprotective, immunocompetent cells of the CNS, Glia 40 (2) (2002) 133–139.
[36] U.K. Hanisch, H. Kettenmann, Microglia: active sensor and versatile effector cells in the normal and pathologic brain, Nat. Neurosci. 10 (11) (2007) 1387–1394.
[37] P. Magni, M. Ruscica, E. Dozio, E. Rizzi, G. Beretta, F.R. Maffei, Parthenolide inhibits the LPS-induced secretion of IL-6 and TNF-α and NF-κB nuclear translocation in BV-2 microglia, Phytother. Res. 26 (9) (2012) 1405–1409.
[38] T. Goldmann, M. Prinz, Role of microglia in CNS autoimmunity, Clin. Dev. Immunol. 2013 (2013) 208093.
[39] Y. He, M. Du, Y. Gao, et al., Astragaloside IV attenuates experimental autoimmune encephalomyelitis of mice by counteracting oxidative stress at multiple levels, PLoS One 8 (10) (2013) e76495.
[40] J. Wang, Z. Ren, Y. Xu, S. Xiao, S.N. Meydani, D. Wu, Epigallocatechin-3-gallate ameliorates experimental autoimmune encephalomyelitis by altering balance among CD4+ T-cell subsets, Am. J. Pathol. 180 (1) (2012) 221–234.
[41] Q. Sun, Y. Zheng, X. Zhang, et al., Novel immunoregulatory properties of EGCG on reducing inflammation in EAE, Front. Biosci. (Landmark Ed) 18 (2013) 332–342.
[42] J. Yan, X. Yang, D. Han, J. Feng, Tanshinone IIA attenuates experimental autoimmune encephalomyelitis in rats, Mol. Med. Rep. 14 (2) (2016) 1601–1609.
[43] X. Yang, J. Yan, J. Feng, Treatment with tanshinone IIA suppresses disruption of the blood-brain barrier and reduces expression of adhesion molecules and chemokines in experimental autoimmune encephalomyelitis, Eur. J. Pharmacol. 771 (2016) 18–28.
[44] R. Martín, J. Carvalho-Tavares, M. Hernández, M. Arnés, V. Ruiz-Gutiérrez, M.L. Nieto, Beneficial actions of oleanolic acid in an experimental model of multiple sclerosis: a potential therapeutic role, Biochem. Pharmacol. 79 (2) (2010) 198–208.
[45] A.A. Abdin, E.A. Hasby, Modulatory effect of celastrol on Th1/Th2 cytokines profile, TLR2 and CD3+ T-lymphocyte expression in a relapsing-remitting model of multiple sclerosis in rats, Eur. J. Pharmacol. 742 (2014) 102–112.
[46] N. Liu, Q.C. Kan, X.J. Zhang, et al., Upregulation of immunomodulatory molecules by matrine treatment in experimental autoimmune encephalomyelitis, Exp. Mol. Pathol. 97 (3) (2014) 470–476.
[47] Q.C. Kan, P. Lv, X.J. Zhang, Y.M. Xu, G.X. Zhang, L. Zhu, Matrine protects neuro-axon from CNS inflammation-induced injury, Exp. Mol. Pathol. 98 (1) (2015) 124–130.
[48] Q.C. Kan, Q.X. Pan, X.J. Zhang, et al., Matrine ameliorates experimental autoimmune encephalomyelitis by modulating chemokines and their receptors, Exp. Mol. Pathol. 99 (2) (2015) 212–219.
[49] S.Q. Liu, M.L. Zhang, H.J. Zhang, et al., Matrine promotes oligodendrocyte development in CNS autoimmunity through the PI3K/Akt signaling pathway, Life Sci. 180 (2017) 36–41.
[50] Y. Zeng, B. Gu, X. Ji, X. Ding, C. Song, F. Wu, Sinomenine, an antirheumatic alkaloid, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalolmyelitis, Biol. Pharm. Bull. 30 (8) (2007) 1438–1444.
[51] D. Zhu, M. Liu, Y. Yang, et al., Ginsenoside Rd ameliorates experimental autoimmune encephalomyelitis in C57BL/6 mice, J. Neurosci. Res. 92 (9) (2014) 1217–1226.
[52] Y. Jiang, A. Wu, C. Zhu, et al., The protective effect of berberine against neuronal damage by inhibiting matrix metalloproteinase-9 and laminin degradation in experimental autoimmune encephalomyelitis, Neurol. Res. 35 (4) (2013) 360–368.
[53] X. Qin, B.T. Guo, B. Wan, L. Fang, L. Lu, L. Wu, et al., Regulation of Th1 and Th17 cell differentiation and amelioration of experimental autoimmune encephalomyelitis by natural product compound berberine, J. Immunol. 185 (3) (2010) 1855–1863.

[54] Y. Wang, Y. Mei, D. Feng, L. Xu, Triptolide modulates T-cell inflammatory responses and ameliorates experimental autoimmune encephalomyelitis, J. Neurosci. Res. 86 (11) (2008) 2441–2449.
[55] B. Adamczyk, M. Adamczyk-Sowa, New insights into the role of oxidative stress mechanisms in the pathophysiology and treatment of multiple sclerosis, Oxidative Med. Cell. Longev. 2016 (2016) 1973834.
[56] L. Haider, M.T. Fischer, J.M. Frischer, et al., Oxidative damage in multiple sclerosis lesions, Brain 134 (Pt 7) (2011) 1914–1924.
[57] M.T. Fischer, I. Wimmer, R. Höftberger, et al., Disease-specific molecular events in cortical multiple sclerosis lesions, Brain 136 (Pt 6) (2013) 1799–1815.
[58] A.H. Bhat, K.B. Dar, S. Anees, et al., Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight, Biomed. Pharmacother. 74 (2015) 101–110.
[59] R. Jha, S.I. Rizvi, Age-dependent decline in erythrocyte acetylcholinesterase activity: correlation with oxidative stress, Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 153 (3) (2009) 195–198.
[60] R. Resende, E. Ferreiro, C. Pereira, C.R. de Oliveira, Neurotoxic effect of oligomeric and fibrillar species of amyloid-beta peptide 1–42: involvement of endoplasmic reticulum calcium release in oligomer-induced cell death, Neuroscience 155 (3) (2008) 725–737.
[61] G. Thinakaran, E.H. Koo, Amyloid precursor protein trafficking, processing, and function, J. Biol. Chem. 283 (44) (2008) 29615–29619.
[62] M.E. Muroski, M.D. Roycik, R.G. Newcomer, et al., Matrix metalloproteinase-9/gelatinase B is a putative therapeutic target of chronic obstructive pulmonary disease and multiple sclerosis, Curr. Pharm. Biotechnol. 9 (1) (2008) 34–46.
[63] D.V. Beckmann, F.B. Carvalho, C.M. Mazzanti, et al., Neuroprotective role of quercetin in locomotor activities and cholinergic neurotransmission in rats experimentally demyelinated with ethidium bromide, Life Sci. 103 (2) (2014) 79–87.
[64] X.L. Hu, Y.X. Niu, Q. Zhang, et al., Neuroprotective effects of Kukoamine B against hydrogen peroxide-induced apoptosis and potential mechanisms in SH-SY5Y cells, Environ. Toxicol. Pharmacol. 40 (1) (2015) 230–240.
[65] D. Wang, S.P. Li, J.S. Fu, S. Zhang, L. Bai, L. Guo, Resveratrol defends blood-brain barrier integrity in experimental autoimmune encephalomyelitis mice, J. Neurophysiol. 116 (5) (2016) 2173–2179.
[66] H.R. Ghaiad, M.M. Nooh, M.M. El-Sawalhi, A.A. Shaheen, Resveratrol promotes remyelination in cuprizone model of multiple sclerosis: biochemical and histological study, Mol. Neurobiol. 54 (5) (2017) 3219–3229.
[67] Y. Du, T.Z. Fischer, L.N. Lee, L.D. Lercher, C.F. Dreyfus, Regionally specific effects of BDNF on oligodendrocytes, Dev. Neurosci. 25 (2–4) (2003) 116–126.
[68] S.K. Karadimas, C.H. Gialeli, G. Klironomos, et al., The role of oligodendrocytes in the molecular pathobiology and potential molecular treatment of cervical spondylotic myelopathy, Curr. Med. Chem. 17 (11) (2010) 1048–1058.
[69] C. Acosta, C. Cortes, K. Altaweel, et al., Immune system induction of nerve growth factor in an animal model of multiple sclerosis: implications in re-myelination and myelin repair, CNS Neurol. Disord. Drug Targets 14 (8) (2015) 1069–1078.
[70] W.W. Wang, L. Lu, T.H. Bao, et al., Scutellarin alleviates behavioral deficits in a mouse model of multiple sclerosis, possibly through protecting neural stem cells, J. Mol. Neurosci. 58 (2) (2016) 210–220.
[71] Y. Zhang, L. Yin, N. Zheng, et al., Icariin enhances remyelination process after acute demyelination induced by cuprizone exposure, Brain Res. Bull. 130 (2017) 180–187.
[72] H.A. Arnett, S.P. Fancy, J.A. Alberta, C. Zhao, S.R. Plant, S. Kaing, et al., bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS, Science 306 (5704) (2004) 2111–2115.
[73] P. Eisele, A. Alonso, M. Griebe, K. Szabo, M.G. Hennerici, A. Gass, Investigation of cerebral microbleeds in multiple sclerosis as a potential marker of blood-brain barrier dysfunction, Mult. Scler. Relat. Disord. 7 (2016) 61–64.
[74] H. Nishihara, F. Shimizu, Y. Sano, et al., Fingolimod prevents blood-brain barrier disruption induced by the sera from patients with multiple sclerosis, PLoS One 10 (3) (2015) e0121488.
[75] S. McQuaid, P. Cunnea, J. McMahon, U. Fitzgerald, The effects of blood-brain barrier disruption on glial cell function in multiple sclerosis, Biochem. Soc. Trans. 37 (Pt 1) (2009) 329–331.
[76] W. Jia, R. Lu, T.A. Martin, W.G. Jiang, The role of claudin-5 in blood-brain barrier (BBB) and brain metastases (review), Mol. Med. Rep. 9 (3) (2014) 779–785.
[77] S.D. Marlin, T.A. Springer, Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1), Cell 51 (5) (1987) 813–819.
[78] J.B. Dietrich, The adhesion molecule ICAM-1 and its regulation in relation with the blood-brain barrier, J. Neuroimmunol. 128 (1–2) (2002) 58–68.
[79] R.L. Dedrick, S. Bodary, M.R. Garovoy, Adhesion molecules as therapeutic targets for autoimmune diseases and transplant rejection, Expert. Opin. Biol. Ther. 3 (1) (2003) 85–95.
[80] A. Minagar, J.S. Alexander, Blood-brain barrier disruption in multiple sclerosis, Mult. Scler. 9 (6) (2003) 540–549.
[81] L.M. Peeters, M. Vanheusden, V. Somers, et al., Cytotoxic CD4+ T cells drive multiple sclerosis progression, Front. Immunol. 8 (2017) 1160.
[82] X.X. Zhao, C. Peng, H. Zhang, L.P. Qin, Sinomenium acutum: a review of chemistry, pharmacology, pharmacokinetics, and clinical use, Pharm. Biol. 50 (8) (2012) 1053–1061.
[83] M.J. Fabis, G.S. Scott, R.B. Kean, H. Koprowski, D.C. Hooper, Loss of blood-brain barrier integrity in the spinal cord is common to experimental allergic encephalomyelitis in knockout mouse models, Proc. Natl. Acad. Sci. U. S. A. 104 (13) (2007) 5656–5661.
[84] S.P. Cramer, H. Simonsen, J.L. Frederiksen, E. Rostrup, H.B. Larsson, Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI, Neuroimage Clin. 4 (2014) 182–189.
[85] S.L. Yates, L.H. Burgess, J. Kocsis-Angle, et al., Amyloid beta and amylin fibrils induce increases in proinflammatory cytokine and chemokine production by THP-1 cells and murine microglia, J. Neurochem. 74 (3) (2000) 1017–1025.
[86] V.W. Yong, Metalloproteinases: mediators of pathology and regeneration in the CNS, Nat. Rev. Neurosci. 6 (12) (2005) 931–944.
[87] D. Kempuraj, R. Thangavel, G.P. Selvakumar, et al., Brain and peripheral atypical inflammatory mediators potentiate neuroinflammation and neurodegeneration, Front. Cell. Neurosci. 11 (2017) 216.
[88] R.J. Franklin, Why does remyelination fail in multiple sclerosis, Nat. Rev. Neurosci. 3 (9) (2002) 705–714.
[89] J.R. Plemel, W.Q. Liu, V.W. Yong, Remyelination therapies: a new direction and challenge in multiple sclerosis, Nat. Rev. Drug Discov. 16 (2017) 617–634.
[90] R.J. Franklin, C. Ffrench-Constant, Remyelination in the CNS: from biology to therapy, Nat. Rev. Neurosci. 9 (11) (2008) 839–855.
[91] J. Xiao, A.W. Wong, M.M. Willingham, et al., BDNF exerts contrasting effects on peripheral myelination of NGF-dependent and BDNF-dependent DRG neurons, J. Neurosci. 29 (13) (2009) 4016–4022.
[92] S. Razavi, G. Nazem, M. Mardani, E. Esfandiari, H. Salehi, S.H. Esfahani, Neurotrophic factors and their effects in the treatment of multiple sclerosis, Adv. Biomed. Res. 4 (2015) 53.