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Neuroprotective natural products against experimental autoimmune encephalomyelitis: A review

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1. Introduction

Multiple sclerosis is a chronic inflammatory demyelinating disease of the CNS which leads to the demyelination in the white and gray matter (Lassmann, 2014). MS is the most frequent neurological disease in young adults between the ages of 20–40 years and approximately affects 2.5 million people around the world (Tullman, 2013). Clinical manifestations of MS typically appear in the thirties and forties, and it affects women almost three times more than men (Constantinescu et al., 2011). It has a high prevalence in regions with high geographic latitudes such as North America and Northern Europe and has low rates in Eastern Asia and sub-Saharan Africa (Emami et al., 2016; Leray et al., 2016). Little is known about the etiology of MS. However, susceptible genes and environmental factors seem to play a role in the pathogenesis of this disease. Blood–brain barrier (BBB) dysfunction, immune cells infiltration into the CNS and antigens attack against the neurons and oligodendrocytes are responsible for the main inflammatory processes. Moreover, several autoimmune mechanisms account for axonal and neuronal degeneration (Ellwardt and Zipp, 2014). Oxidative stress which leads to mitochondrial damage is also a major factor in demyelination and neurodegeneration in MS patients (Lassmann, 2014). MS is considered to be a predominantly T cell-mediated autoimmune disease as supported by evidence derived from its principal model, experimental autoimmune encephalomyelitis (EAE) (Stadelmann et al., 2011). EAE is the animal model used for evaluating inflammatory demyelinating disease of the CNS. It is induced by triggering an immune response against myelin and has been used extremely as a prototype of Th1- and/or Th17-driven organ-specific autoimmune conditions and as an animal model for multiple sclerosis (Rao and Segal, 2012). EAE experimental model has already led directly to the development of four FDA-approved medicines for the treatment of MS: glatiramer acetate, mitoxantrone, natalizumab (Leuschner et al., 1986) and fingolimod.

Natural products are defined as organic compounds that are produced by living systems. Their structure elucidation and biosynthesis are among the popular fields in organic chemistry. Natural products can be classified into three categories i.e. primary metabolites (nucleic acids, amino acids and sugars), cellular structure forming compounds (cellulose, lignins and proteins) and secondary metabolites. Most primary metabolites play their pharmacological role in the organism or cell that has produced them, whilst, secondary metabolites are able to biologically affect other organisms (Hanson, 2003). A tremendous investigation on the effectiveness of pure compounds and plant extracts in slowing the progression of EAE has resulted in the identification of valuable lead compounds and drugs. Gilenya® (fingolimod) is the first oral treatment for relapsing multiple sclerosis that has been derived from myriocin-a metabolite of the fungus *Isaria sinclairii* (Miyake et al., 1995)-by SAR studies to determine the active parts of the molecule. Other extracts and natural products specifically *Cannabis*-based drugs are being studied in clinical trials as well.

Here in this review, we have summarized the mechanisms of natural products as well as plant powders, extracts and essential and fatty oils in treating inflammatory and immunological processes involved in the pathogenesis of EAE.

2. Pathogenesis of multiple sclerosis

The mechanisms of neurodegeneration in MS are not well understood yet. Demyelination, axonal injury and chronic inflammation occur in both relapsing and progressive stage of the disease (Haider et al., 2011) It is believed that MS is primarily caused by increased migration of autoreactive T lymphocytes (T cells) through a disrupted BBB (Compston and Coles, 2008). The T cells recognize and attack the myelin sheath, resulting in the formation of demyelinated lesions in the brain and spinal cord which in turn leads to the impairment of nerve conduction and axonal loss (Babbe et al., 2000). The most important morphological trait of MS is demyelination of axons leading to the blockade or slowing of signal conduction at the site of demyelination. Neurological symptoms gradually appear after involvement of a significant proportion of axonal fibers within a specific pathway (Fletcher et al., 2010). Generally, key players of neurodegeneration in MS include microglia activation, mitochondrial damage in axons, chronic oxidative injury, and iron accumulation in the brain (Mahad et al., 2015).

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Microglia are resident glial cells in the CNS, that normally remove the damaged neurons by phagocytosis. However, the chronic activation of microglia may result in neuronal damage by releasing cytotoxic molecules including proinflammatory cytokines, ROS, proteinases and complement proteins. Accordingly, suppression of microglia-mediated inflammatory response would be an important therapeutic strategy in the treatment of neurodegenerative diseases (Dheen et al., 2007). Excessive ROS, primarily generated by macrophages, is also the key element in the pathogenesis of MS through mediating oligodendrocytes injury, neurons demyelination and axonal damage (Haider et al., 2011; Gilgun-Sherki et al., 2004). Mitochondrial injurycan be triggered by ROS and NO (Haider et al., 2011). Mitochondria are the most efficient ATP generators and are crucial players in many cellular processes such as fatty acid oxidation, apoptosis, and calcium homeostasis. Therefore, mitochondrial injury may result in energy deficit, chronic cell stress and an increase in the susceptibility of axons to excitotoxic injury through high levels of calcium ions entrance into the neurons (Mahad et al., 2009). Age-related iron deposition is an important factor in the pathophysiologic changes that happen especially in the neurodegenerative processes of MS (Ge et al., 2007). Nonheme iron is the most form of iron that deposits in oligodendrocytes and myelin, the primary target of inflammatory activities in MS (Hametner et al., 2013). Quantitative evaluation of iron content has indicated its enhanced accumulation in the deep gray matter of MS patients (Ge et al., 2007). Pathological and MRI studies revealed that iron deposits at the edges of chronic MS lesions. Also, injecting iron-containing ferritin into the rat spinal cord promotes the formation and differentiation of oligodendrocyte from OPCs (Hametner et al., 2013). Therefore, iron-chelating therapies for MS patients may not be of therapeutic utility.

EAE was first described in 1930s and is still widely used as an experimental model of MS. Typically, sensitization to myelin antigens in EAE happens by using an adjuvant, consisting of bacterial components that are extremely capable of triggering the innate immune system through pattern recognition receptors (Constantinescu et al., 2011). The EAE pathogenic events have been summarized as follows:

In the peripheral blood circulation, T cells become activated as a result of an encounter to an infectious antigen or a superantigen (microbial antigens with potent T cell stimulatory effect) (Fletcher et al., 2010; Kotzin et al., 1993). Activated T cells can produce inflammatory cytokines and are capable of being differentiated into Th1 or Th17 cells (Constantinescu et al., 2011). They can also up-regulate integrins such as VLA-4 that are necessary for leukocytes adhesion to VCAM-1 on the inflamed endothelium leading to the leukocytes extravasation through the BBB (Leger et al., 1997). Then B cells, monocytes and macrophages reach the CNS by crossing the permeabilized BBB and encounter the antigens probably derived from myelin. As a result, autoreactive T cells reactivate, differentiate and produce inflammatory cytokines including IFN-γ, and some interleukins (IL-17, IL-22, IL-21) that attract more inflammatory cells into the CNS (Constantinescu et al., 2011). B cells can contribute to the pathology of EAE, via complement activation, cytokine cytotoxicity and generation of nitric oxide, ROS and reactive nitrogen species (Hemmer et al., 2006). Consequently, myelin destruction, lack of regeneration potential and axonal injury can lead to neuronal death followed by the appearance of EAE symptoms.

3. Pharmacology

3.1. Flavonoids

Flavonoids are naturally occurring polyphenolic compounds found in many plants. The basic structure of flavonoids consists of 15-carbon skeleton containing two fused rings, named A and B linked via an oxygen-containing heterocyclic C ring (Raffa et al., 2017). Flavonoids display several biological activities including anti-oxidant, anti-microbial, anti-cancer, anti-angiogenic, immunomodulatory, anti-allergic (Shakeri et al., 2016), and neuroprotective in neuronal insults (Haghmorad et al., 2017). Flavonoids have positive effects during the pathogenesis of MS and EAE because of their potent inhibitory effect on proliferation of auto antigen specific T cells and IFN-γ production (Verbeek et al., 2005). *Capparis ovata*, as a rich source of flavonoids, suppressed the development of EAE in C57BL/6 mice via down-regulating some inflammatory genes such as IL-6, CCL5, CXCL10, CXCL9, NF-κB, and TNF-α (Ozgun-Acar et al., 2016).

3.1.1. Hesperidin

Hesperidin (3,5,7-trihydroxy flavanone-7-rhamnoglucoside), is a flavonoid glycoside isolated from the rinds of some *Citrus* species such as sweet orange and lemon (Sun et al., 2017). Considering the important role of oxidative stress in the pathogenesis of EAE, hesperidin as a strong anti-oxidant flavonoid, may show neuroprotective activity in diseases like MS. Hesperidin prevents the oxidative stress, decreases lipid peroxidation and inhibits immunological and histological damage caused by EAE (Ciftci et al., 2015). EAE development in C57BL/6 mice can be suppressed by hesperidin in a dose-dependent manner via reducing proinflammatory cytokines (TNF-α, IL-6 and IL-17) and evoking the polarization of $CD4^+$ T cells to regulatory T cells. This inhibits autoreactive T cells proliferation and migration into the CNS (Haghmorad et al., 2017).

3.1.2. Genistein

Genistein (4′,5,7-trihydroxy isoflavone), an isoflavone with phytoestrogenic properties, has different biological effects including anticancer, anti-angiogenic, anti-oxidant, anti-inflammatory, anti-nociceptive and neuro-protective (Hu et al., 2017). Genistein oral administration in the early phase of EAE, decreased the severity of the disease via inhibiting T cells proliferation, decreasing IFN-γ, IL-12 and TNF-α (Jahromi et al., 2014) and increasing IL-10 secretion (Jahromi et al., 2014; Razeghi et al., 2009). A lipophilic analog of genistein has reduced CTLA-4 expression, elevated IL-10 production and decreased IFN-γ and IL-6 as well (Castro et al., 2012).

3.1.3. Silymarin

Found in the seeds of *Silybum marianum*, this flavanolignan mixture includes silibinin, isosilibinin, silicristin and silidianin. In a study by Gharagozloo et al., silymarin had immunosuppressive effects through PI3K/Akt/mTOR pathway by preventing the phosphorylation of p70S6K and p-S6 proteins (Gharagozloo et al., 2013). Silymarin is able to suppress the secretion of Th1 related cytokines such as IL-2, IFN-γ, and TNF-α (Gharagozloo et al., 2010; Esmaeil et al., 2017). It has been shown that silibinin, as one of the main bioactive compounds of silymarin, has significant effects on EAE through reducing histological signs of inflammation and demyelination, down-regulating the secretion of proinflammatory Thl cytokines *in vivo* and up-regulating Th2 cytokines *in vitro* (Min et al., 2007).

3.1.4. Naringenin

Naringenin was found effective in delaying the seizure onset, ameliorating induced morphological brain alterations, and protecting neurons in the model of Alzheimer's and Parkinson's disease (Hegazy et al., 2016; Copmans et al., 2017). This compound attenuates the symptoms of EAE and lowers demyelination and cell infiltration in the spinal cord. Besides, decreased Th1, Th9, and Th17 cells and their transcription factors T-bet, PU.1, and ROR-γt were observed in the CNS of naringenin-treated EAE mice (Wang et al., 2018a).

3.1.5. Baicalin

Baicalin has been isolated from the roots of *Scutellaria baicalensis*, a plant widely used in Asia for treating inflammation, hypertension and viral and bacterial infections (Li-Weber, 2009). This compound can suppress EAE development in SJL/J mice and rats through inhibiting IFN-γ, inducing IL-4 (Zeng et al., 2007a) and promoting inflammatory cells apoptosis in the spinal cord (Xu et al., 2011). It also regulates Th1

and Th17 cells differentiation and activity with no effects on Th2, Treg cells and IL-4 levels (Zhang et al., 2015).

3.1.6. Icariin

Icariin is a flavonoid glucoside that is isolated from *Epimedium* spp (Berberidaceae) (Shen et al., 2015) and is considered as a primary active compound of *Epimedium* extracts with neuroprotective and estrogen-like effects (Becher et al., 2002). Thus, it may have a therapeutic role in treating neurodegeneration (Zhang et al., 2014a). Icariin can decrease IL-17 and IFN-γ expression in the CNS and peripheral lymphoid organs of mice (Shen et al., 2015). It alleviates inflammatory infiltration and decreases BBB leakage of paracellular tracer either (Shen et al., 2015). Icariin has a role in oligodendrogenesis promotion, neurotrophic factors expression enhancement and axonal remyelination (Zhang et al., 2017). A recent study by Wei et al. represented the synergy between icariin and methyl prednisolone in reducing the levels of IL-17 and corticosterone concentration, up-regulating glucocorticoid receptor expression in cerebral white matter and increasing anti-apoptotic and anti-inflammatory effects of methyl prednisolone. This synergy might help to reduce methyl prednisolone dose and side effects for EAE treatment (Wei et al., 2015).

3.1.7. Epimedium flavonoids

Epimedium flavonoids (EF) are derived from *Epimedium brevicornum* (Berberidaceae). Intragastric administration of EF in rats has reduced the EAE clinical score, alleviated demyelination, prevented astrocyte activation and protected the myelin sheath (Yin et al., 2012). EF treatment has led to a reduced myelin breakdown in the corpus callosum of cuprizone-induced demyelination in C57BL/6 mice (Liang et al., 2015). Therefore, as natural compounds with neuroprotective effects, *Epimedium* flavonoids worth further investigation as potential anti-MS drugs.

3.2. Licochalcone A

Licochalcone A is an oxygenated chalcone that can be obtained from the roots of *Glycyrrhiza* spp, specially from *Glycyrrhiza inflata*. This compound may be able to prevent the inflammatory processes involved in EAE since it can inhibit IFN-γ and TNF-α (Barfod et al., 2002; Chu et al., 2012), reduce iNOS induction (Furusawa et al., 2009) and hinder STAT-3 activation (Funakoshi-Tago et al., 2008). Fontes et al. reported that *in vitro* treatment of EAE mice splenocytes by licochalcone A inhibits IFN-γ, IL-17, TNF-α, H_2O_2 and NO production; also, *in vivo* treatment reduces the clinical score, disease severity and IL-17, IFN-γ and TNF-α in the peritoneal cells (Fontes et al., 2014).

3.3. Curcumin

Isolated from the rhizomes of turmeric (*Curcuma longa*), curcumin has been used as a coloring and flavoring spice in foods as well as a wound healing agent for centuries (Xie et al., 2009). Some studies have reported the ameliorative effect of curcumin on EAE by reducing IL-6, IL-21 and Th17 cells differentiation (Xie et al., 2009). Curcumin can lower IL-12 and IL-23 secretion as well as IFN-γ and IL-17 in the CNS and lymphoid organs (Kanakasabai et al., 2012). A dose-dependent decrease in the secretion of IFN-γ, IL-12, IL-17 and IL-23 was observed after *ex vivo* and *in vitro* treatment of cultured spleen cells with curcumin. The EAE ameliorative effect of this compound was also found to be associated with an up-regulation of IL-10, PPAR-γ and $CD4^+CD25+$- Foxp3+ Treg cells in the CNS and lymphoid organs (Kanakasabai et al., 2012). Curcumin can also inhibit the apoptosis in the spinal cord both in the acute and chronic stage of EAE by preventing the expression of activated caspase 3, caspase 9 and cytochrome-c (Feng et al., 2014).

3.4. Arctigenin

Arctigenin from *Arctium lappa*, represents its anti-inflammatory effects through suppressing proinflammatory cytokines (Li et al., 2016a). This compound can inhibit Th1 and Th17 cells in peripheral immune organs *in vivo* as well as IFN-γ, IL-17A and IL-17F both *in vitro* and *in vivo* (Li et al., 2016a). The ability of arctigenin for AMPK activation, PPAR-γ up-regulation, phosphorylated p38 inhibition and ROR-γt suppression prevents Th17 cells differentiation and ameliorates EAE (Li et al., 2016a).

3.5. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a stilbenoid compound that possess C6–C2–C6 structure. Stilbenoids are a group of phytoalexins which are found in several plant species, grapes, mulberries, nuts and teas (Dvorakova and Landa, 2017). They are known for diverse biological effects including anti-inflammatory, anti-tumor, anti-atherogenic, anti-viral and, more recently, neuroprotective effects (Riviere et al., 2012). Resveratrol, is well known for its anti-inflammatory, anti-cancer, anti-oxidant, anti-aging and anti-microbial activities with no major side effects (Wang et al., 2016). The neuroprotective activities of this compound in neurodegenerative and immune-mediated diseases is through decreasing IL-2, IL-6, IL-8, IL-12, IFN-γ, TNF-α, and GM-CSF (granulocyte-macrophage colony-stimulating factor) (Ghaiad et al., 2017; Imler and Petro, 2009). Sometimes, the risk of autoimmune diseases like EAE and MS is increased when the activity of the effector cells such as Th17 is excessive and not balanced by regulatory cells. It was reported that although resveratrol increases the development of Th17, it also increases the development of regulatory T cells in the CNS (Petro, 2011). Resveratrol reduces the severity of EAE by increasing the development of lymphocyte subsets, $IL-17^+/IL-10^+$ T cells and $CD4^-/IFN-\gamma^+$ cells, repressing macrophage IL-6 expression and enhancing the expression of IL-17 (Imler and Petro, 2009). Wight et al. reported that resveratrol suppresses the development of EAE via preventing the development of Th1 and Th17 cells (Wight et al., 2012). SIRT1, a member of the sirtuin family proteins, is a mammalian deacetylase with a key role in innate immunity through the suppression of proinflammatory cytokines production in dendritic cells and macrophages (Jia et al., 2018). The neuroprotective effect of SRT501 (a pharmaceutical formulation of resveratrol) in EAE optic nerves and spinal cords was attributed to activating SIRT1 accompanied by promoting neuronal survival and suppressing apoptotic pathways (Shindler et al., 2010). Similarly, SRT501 prevents neuronal damage in chronic EAE (Fonseca-Kelly et al., 2012). In contrast, Sato et al. have reported that resveratrol significantly exacerbates demyelination and inflammation with no neuroprotection in the central nervous system in EAE models that may be related to the enhanced infiltration of inflammatory cells across the blood brain barrier (Sato et al., 2013).

3.6. Plumbagin

Plumbagin is a bicyclic naphthoquinone found in the roots of *Plumbago zeylanica*. It can also be isolated from the plants of Dioncophyllaceae, Droseraceae, Plumbaginaceae and Ancistrocladaceae. Plumbagin controls encephalitogenic T cell responses and ameliorates mouse EAE through down-regulation of JAK/STAT pathway. It selectively inhibits IFN-γ and IL-17 production by $CD4^+$ T cells via inhibiting the phosphorylation of JAK1 and JAK2. Plumbagin suppressed STAT1/STAT4/T-bet pathway as well as STAT3/ROR pathway which are critical for Th1 and Th17 differentiation, respectively. Moreover, it suppressed proinflammatory molecules such as iNOS, IL-6 and IFN-γ, and inhibited IkBα degradation and phosphorylation (Jia et al., 2011). Plumbagin hinders the differentiation, maturation, and function of human monocyte-derived DCs and restricts the expression of Th1- and Th17-polarizing cytokines in mature DCs. This

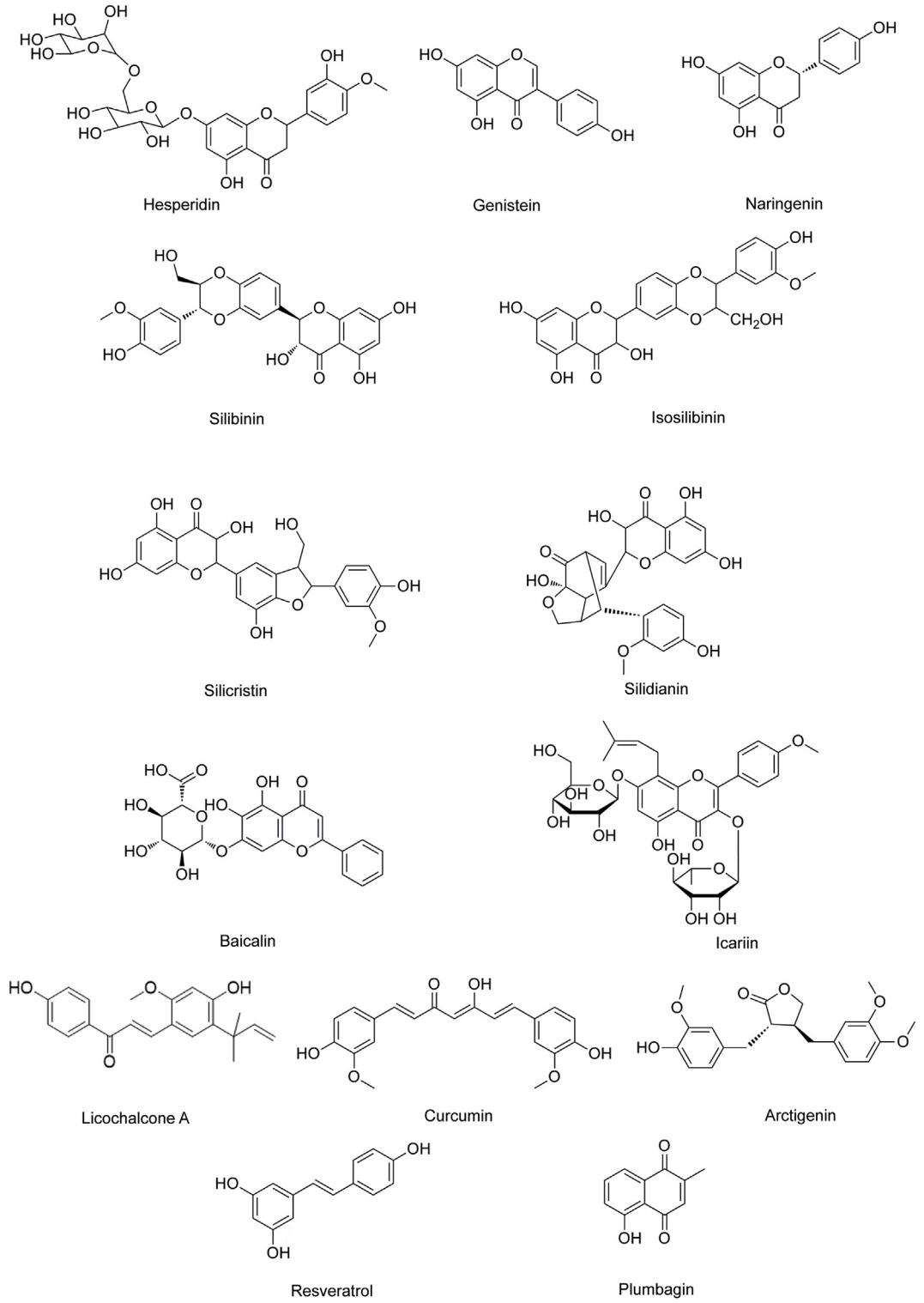

Fig. 1. Phenolic compounds (flavonoids, chalcones, diarylheptanoids, lignans, stilbenoids, and quinones) with EAE ameliorative activity in animal models.

compound has improved the clinical severity of EAE in mice, including CNS inflammation and spinal demyelination (Zhang et al., 2014b). Fig. 1 demonstrates the chemical structures of flavonoids, chalcones, diarylheptanoids, lignans, stilbenoids and quinones with neuroprotective and EAE ameliorative activity.

3.7. Glucomoringin

Glucomoringin (GMG) (Fig. 2), which is mostly found in the seeds of *Moringa oleifera* (Moringaceae) is a glucosinolate compound that releases moringin (glucomoringin isothiocyanate) through a hydrolysis reaction catalyzed by myrosinase enzyme. A recent study has demonstrated the ability of moringin to ameliorate EAE through a decrease in TNF-α expression and ROS generation. It is able to attenuate the histological EAE score, demyelination, axonal loss and cellular apoptotic death mechanisms (Galuppo et al., 2014). Further, pre-treating EAE mice with this compound has reversed the abnormal Wnt-β-catenin signaling, leading to a lower GSK3β and CK2α levels and thus

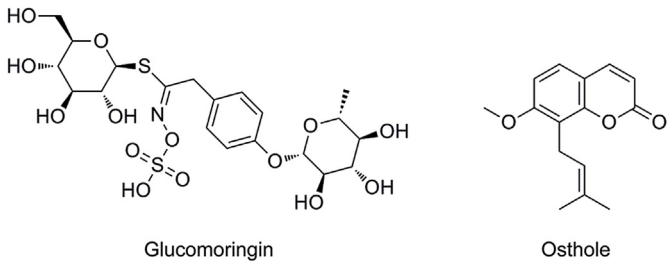

Fig. 2. The glucosinolate compound, glucomoringin (left) and coumarin compound, osthole (right) with EAE ameliorative activity in animal models.

suppressed the activation of EAE-associated regulatory T cells (Giacoppo et al., 2016). It has also reduced the proinflammatory mediators IL-6, IL-1β and COX2 due to the up-regulation of PPARγ expression (Giacoppo et al., 2016).

3.8. Osthole

Osthole (7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one) (Fig. 2), is one of the active coumarin compounds identified in the plant *Cnidium monnieri* (Wang et al., 2018b). Anti-inflammatory, immuno-modulatory and neuroprotective activities of osthole has been shown in inflammatory diseases like arthritis and hepatitis (Li et al., 2014). The effects of osthole on EAE demyelination were investigated by Chen et al. They have shown that osthole retarded the disease onset and attenuated the clinical severity along with the reduction of NGF and inhibition of IFN-γ expression in EAE mice (Chen et al., 2010). It was also shown that bone marrow derived neural stem cells (BM-NSCs) transplantation plus osthole pre-treatment suppressed EAE and showed significant advantages over conventional BM-NSC therapy (Gao et al., 2014).

3.9. Alkaloids

Structurally, more than 3000 alkaloids have been identified from plants. These nitrogen-containing compounds are most commonly derived from amino acid starting materials (Dey et al., 2018). Some alkaloids have demonstrated anti-inflammatory activities through suppressing inflammatory cytokines, inhibiting NF-κB activation and attenuating inducible nitric oxide synthase and cyclooxygenase-2 (Hardardottir et al., 2015). The chemical structures of alkaloids with EAE ameliorative effect has been demonstrated in Fig. 3.

3.9.1. Huperzine A

Huperzine A is a sesquiterpene alkaloid that is isolated from *Huperzia serrata*. This compound ameliorates EAE through down-regulating mRNA levels of the IFN-γ, IL-17 and proinflammatory chemokines (MCP-1, RANTES, and TWEAK) and up-regulating anti-inflammatory cytokines (IL-4 and IL-10) in the spinal cords of EAE mice (Wang et al., 2012). In another study by Tian et al., huperzine A improved the clinical signs of EAE by lowering the chemokine CCL2 production and proinflammatory cytokines expression (TNF-α, IL-6, and IL-1β) in the spinal cords of EAE mice (Tian et al., 2013).

3.9.2. Matrine

Matrine is able to decrease demyelination and inflammation in EAE through different mechanisms such as suppressing the production of proinflammatory cytokines IL-2, IL-6, TNF-α (Cheng et al., 2006; Li et al., 2010; Zhang et al., 2008), IL-17 and IL-23 (Zhao et al., 2011). This compound reduces the expression of CCL3, CCL5, ICAM-1, VCAM-1, TLR4 and MD-2 (Kan et al., 2013) and regulates glutamate-related molecules (Kan et al., 2014). Other EAE ameliorative mechanisms comprise improving BBB integrity (Zhang et al., 2013), reducing oligodendrocytes apoptosis (Zhu et al., 2016) and preventing neuroaxonal injury. Matrine is able to reduce serum myelin antigens, the effect that is beneficial for continuous CNS attacks inhibition (Ellwardt and Zipp, 2014).

3.9.3. Berberine

Berberine can be isolated from many Berberidaceae species like *Berberis* and *Coptis*. It is used as an anti-inflammatory agent especially for the inflammation of the oral cavity in the Chinese herbal medicine (Kuo et al., 2004). Oral administration of berberine at the disease onset can be effective in reducing demyelination, severity and clinical score of EAE. It alleviates the permeability of BBB by suppressing the enhanced expression of MMP-9 in the brain and CSF of EAE mice (Ma et al., 2010). Berberine can regulate the activation and differentiation of Th17 and to a lesser level Th1 cells (Qin et al., 2010), reduce IκB and P65 phosphorylation and suppress IL-6 production (Qin et al., 2010).

3.9.4. Berbamine

This alkaloid compound from *Berberis vulgaris* has inhibited IFN-γ in $CD4^+$ T cells and decreased T cell proliferation in EAE mice (Ren et al., 2008). It is worth considering that this compound has no therapeutical effects on IFN-γ receptor gene knockout mice, therefore, IFN-γ antagonism might be the possible mechanism of berbamin beneficial outcomes (Ren et al., 2008).

3.9.5. Sinomenine

Sinomenine from *Sinomenium acutum* ameliorates EAE via decreasing the expression levels of both TNF-α and IFN-γ and increasing the CC chemokines including RANTES, MCP-1, and MIP-1α in the spinal cord (Zeng et al., 2007b). It reduces iNOS production in the spinal cord of EAE rats by T-bet/IFN-γ suppression (Gu et al., 2012). A new derivative of sinomenine (1032) improves EAE symptoms by lowering encephalitogenic T cells responses and suppressing Th17, IFN-c and TNF-α (Yan et al., 2010).

3.10. Terpenoids

Terpenoids, as the largest and most diverse group of natural products, possess the anti-bacterial, anti-inflammatory and anti-tumor activities (de las Heras and Hortelano, 2009). Considering the number of building blocks, terpenoids are categorized as hemi-, mono-, sesqui-, di-, ses-, tri-, tetra- and poly-terpenoids that have 5, 10, 15, 20, 25, 30, 40 and > 45 carbons in their structures, respectively (Ku and Lin, 2013). The immunomodulatory activity of some monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, and saponins (Fig. 4) has been reported.

3.10.1. Cornel iridoid glycosides

Cornel iridoid glycosides (CIG) are a type of monoterpenoids in the general form of cyclopentanopyran. Intragastric administration of CIG alleviates EAE by delaying the onset and reducing its severity and incidence (Yin et al., 2014). This effect is mediated through different mechanisms such as preventing microglia activation and NF-κB expression, promoting remyelination (Yin et al., 2014) as well as blocking the down-regulation of BDNF and NGF expression in the spinal cord (Qu et al., 2016).

3.10.2. Thymoquinone

Isolated from the oil of *Nigella sativa* seeds, this compound has demonstrated EAE ameliorative effects. Mohamed et al. have shown that thymoquinone administration is able to improve EAE symptoms in Lewis rats through increasing GSH level in the spinal cord and as a consequence decreasing oxidative stress. Thymoquinone-treated rats had no perivascular inflammation and exhibited mild or improved clinical symptoms (Mohamed et al., 2003). Another study by Spate et al. has shown similar effects in C57BL/6 J mice. Thymoquinone treatment in these animals resulted in an increased GSH level and

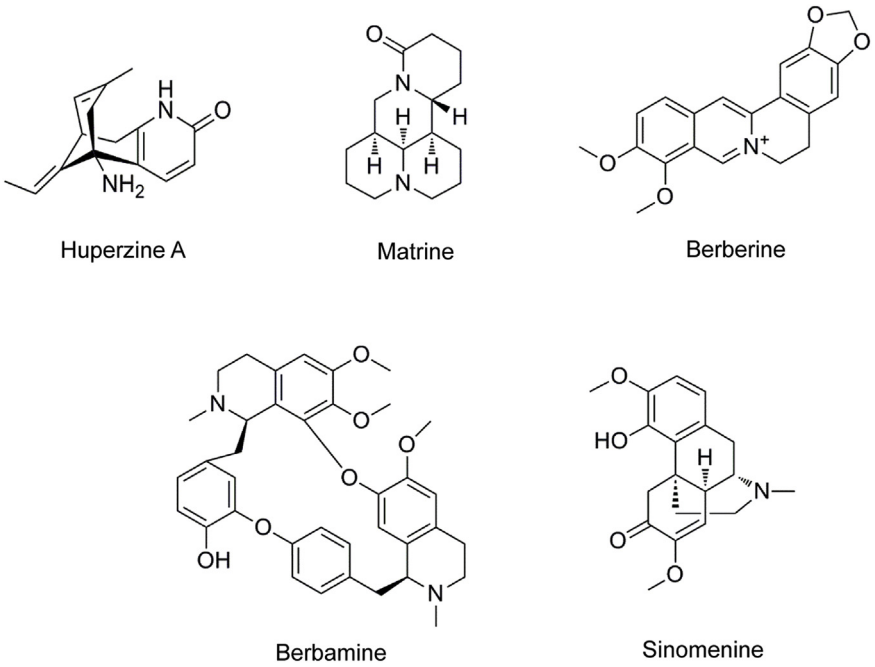

Fig. 3. Alkaloid compounds with EAE ameliorative activity in animal models.

reduced clinical symptoms (Spate et al., 2010).

3.10.3. Carvacrol

As a phenolic monoterpene, carvacrol reduces IFN-γ, IL-6 and IL-17 production in splenocytes and enhances the anti-inflammatory cytokines TGF-β, IL-4 and IL-10 production. Carvacrol-treated mice indicate a lower body weight loss and decreased inflammatory infiltration into the spinal cord that leads to EAE amelioration (Mahmoodi et al., 2019a).

3.10.4. β-Elemene

Elemene is an anti-tumor drug found in the ginger plant *Rhizoma zedoariae.* There is a combination of α-, β- and δ-elemene in the extract of elemene, however, the β isoform is the main component (Zhang et al., 2010). β-elemene exerts anti-cancer effects (Fu, 1984; Tan et al., 2000; Wang et al., 1996) and is able to improve immunity (Wu et al., 1999). A recent study has shown its potency to ameliorate the course of EAE in C57BL/6 mice (Zhang et al., 2011). β-elemene has the ability to inhibit ROR-γt, IL-23 and IL-6 production both *in vivo* and *in vitro*, which is considered as a regulatory mechanism in this disease. A decrease in IL-6 production can inhibit the differentiation of Th17 cells as well (Zhang et al., 2011). It can promote regulatory T cells expansion which may play a key role in decreasing peripheral immune response to myelin oligodendrocyte glycoprotein (MOG) (Zhang et al., 2011). These effects result in less severe neurological deficits and abnormalities (Zhang et al., 2011).

3.10.5. Artemisinin

Artemisinin, a sesquiterpene lactone isolated from *Artemisia annua*, is best known for its anti-malarial activity due to the peroxide bridge (Yao et al., 2016). Artemisinin and its analogues not only possess anti-malarial activity, but also other pharmacological effects that are beneficial especially in treating immune-related diseases (Yao et al., 2016). For example, SM933, a derivative of artemisinin, is able to prevent NF-κB activity and regulate the Rig-G/JAB1 pathway that prevents encephalitogenic T cells proliferation (Wang et al., 2007). SM934, a water soluble derivative, has been effective for autoimmune responses in systematic lupus erythematosus (Hou et al., 2011, 2012). SM934 treatment ameliorates EAE by increasing Treg cells differentiation and expansion besides preventing Th1 and Th17 responses (Li et al., 2013).

3.10.6. β-caryophyllene

β-caryophyllene has potential anti-inflammatory (Veiga et al., 2007), neuroprotective (Assis et al., 2014) and analgesic (Klauke et al., 2014) properties. It has been shown that *(E)*-β-caryophyllene is a major constituent in the *Cannabis* essential oil; this may help to the effect of *Cannabis* preparations, such as Sativex® in managing the neuropathic pain of MS (Gertsch et al., 2008). Fontes et al. indicated the immunomodulatory effects of β-caryophyllene both *ex vivo* and *in vivo*. They showed that treating fresh splenocytes of EAE mice with this compound at 20 and 40 μM can significantly prevent the production of H_2O_2, NO and inflammatory cytokines such as IFN-γ, TNF-α and IL-17. β-caryophyllene decreases the clinical score, inhibits the production of inflammatory cytokines, reduces inflammatory infiltration into the CNS and ameliorates the neurological damages of EAE mice (Fontes et al., 2017).

3.10.7. Triptolide

Triptolide is a diterpenoid triepoxide and the major active compound of *Triptergium wilfordii* (Fu et al., 2006; Kizelsztein et al., 2009; Wang et al., 2008). Intraperitoneal (i.p.) administration of this compound reduces demyelination and inflammation in the CNS of mice. This action is mediated through several mechanisms such as preventing mRNA expression of Th1/ThIL-17 and Th2 cytokines in spleen mononuclear cells and spinal cord tissues, up-regulating Foxp3 expression and preventing NF-κB nuclear translocation (Wang et al., 2008).

Triptolide can prevent IFN-γ production and decrease the expression of IL-12, IL-6 and TNF-α (Chitnis and Khoury, 2003; Powell et al., 1990; Samoilova et al., 1998).]. mRNA expression of IL-23 and IL-17 has been down-regulated by this compound leading to an inhibition in multiple inflammatory pathways and T cell activation, respectively (Wang et al., 2008). Oral administration of triptolide reduces *in vivo* mRNA expression of Th1/Th17 cytokines significantly. It also induces biased Th2 immunity and attenuates inflammatory Th1/Th17 immune responses in the CNS. Protein levels and HSP70 gene transcript increase significantly in the CNS of EAE animals treated with triptolide, which can be a good strategy to confront neurodegenerative diseases (Kizelsztein et al., 2009). HSPs can also regulate general immune response (Pockley,

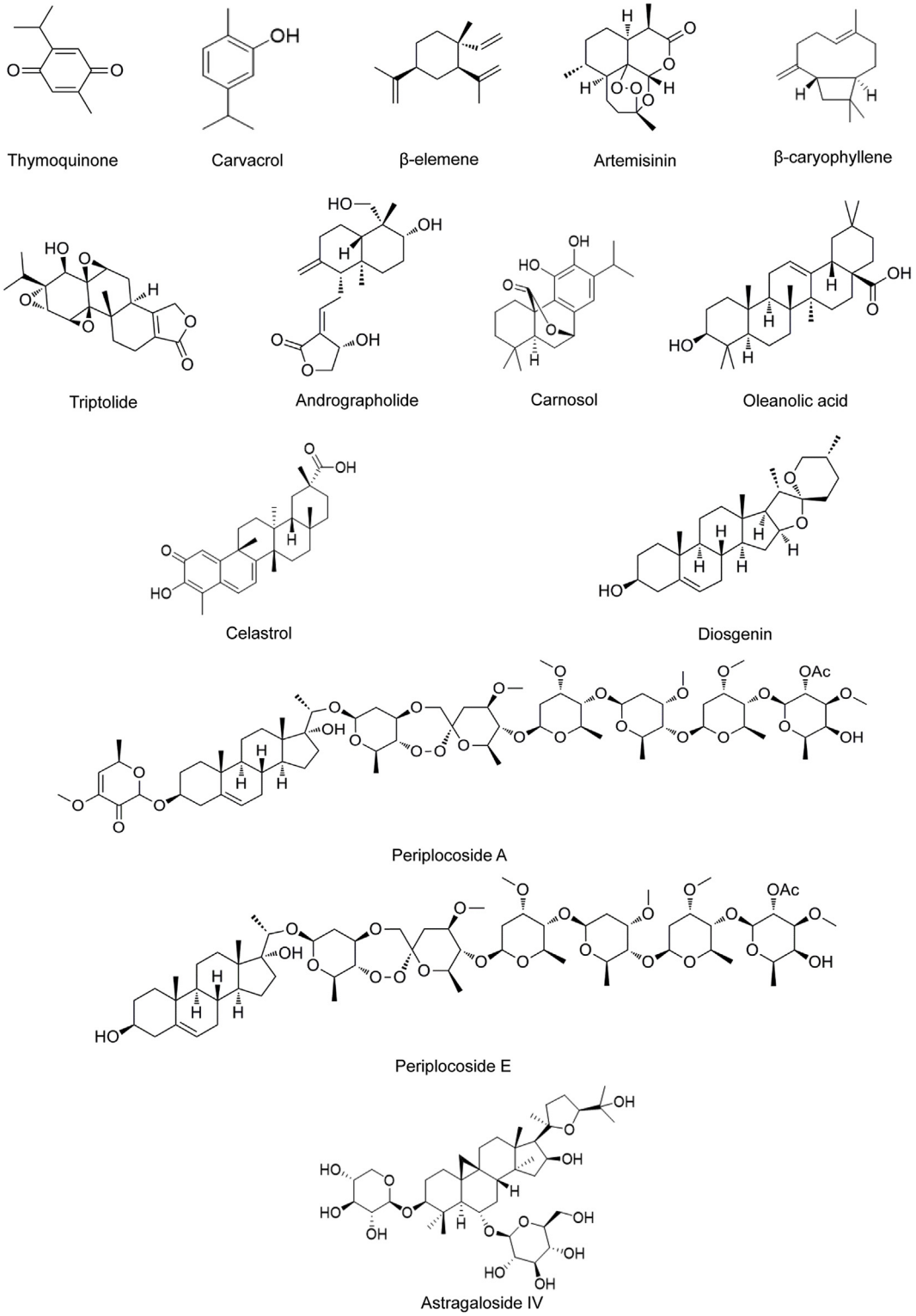

Fig. 4. Terpenoid and saponin compounds with EAE ameliorative activity in animal models.

2003), neuroprotection and tissue repair in EAE (Galazka et al., 2006; Ousman et al., 2007). However, triptolide further medical and clinical application is limited because of its toxicity (Hikim et al., 2000; Huynh et al., 2000). (5R)-5-hydroxytriptolide also called LLDT-8 has been synthesized from triptolide and possesses immunosuppressive activity and less cytotoxicity (Zhou et al., 2005). It suppresses the production of IL-6 and TNF-α or other factors such as nitric oxide in the macrophages (Zhou et al., 2005, 2006) which can help to the therapeutic effects of LLDT-8.

3.10.8. Andrographolide

Andrographolide is the major diterpenoid component of *Andrographis paniculata* extract (Iruretagoyena et al., 2005) and has a regulatory effect on immune responses (Calabrese et al., 2000; Rajagopal et al., 2003). It is able to inhibit DCs function that results in a down-modulation of T cell-mediated immunity in C57BL/6 mice

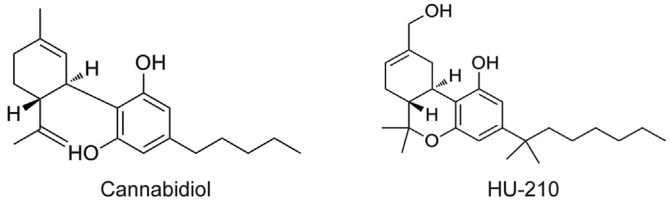

Fig. 5. Cannabinoid compounds with EAE ameliorative activity in animal models.

(Iruretagoyena et al., 2005). Previous studies showed that andrographolide reduces the incidence and also clinical severity of EAE in the early phase (Iruretagoyena et al., 2005). Lower IFN-γ and IL-2 release in response to myelin oligodendrocyte glycoprotein, has been observed in andrographolide-treated mice (Iruretagoyena et al., 2005). Andrographolide may impair the generation of peptide-MHC complexes and reduce the efficiency of DC maturation (Iruretagoyena et al., 2005). It can also bind directly to p50 and inhibit NF-κB dimerization (Xia et al., 2004) which impairs the capacity of DCs to stimulate effector T cells and increases their tolerogenic properties. All these mechanisms result in the EAE amelioration (Iruretagoyena et al., 2006).

3.10.9. Carnosol

Carnosol significantly decreases demyelination process, inflammatory cells infiltration into the CNS, Th17 cells differentiation, and encephalitogenicity in the acute stage of EAE. In the chronic phase, carnosol changes the phenotypes of infiltrated macrophage/microglia to the immunoregulatory ones and induce myelin protein regeneration (Li et al., 2018). However, there is only a rare inflammatory infiltration in the CNS of both PBS- and carnosol-treated mice, proposing that neuroinflammation is not the major pathogenesis in the chronic stage (Li et al., 2016b).

3.10.10. Oleanolic acid

Oleanolic acid (OA) and OA containing extracts exert immunomodulatory properties and ameliorate neuroinflammation and EAE (Tran et al., 2008; Martin et al., 2010). OA and erythrodiol, two natural triterpenes, improve EAE symptoms in C57BL/6 mice by inhibiting leptin production, decreasing the leukocytes infiltration into the CNS, increasing anti-inflammatory cytokines levels and suppressing IL-17 and IFN-γ expression in the spinal cord (Martin et al., 2012). OA synthetic derivative, CDDO-TFEA, has led to a significant alleviation of EAE clinical symptoms as well. This effect was mediated by inducing Nrf2 expression and signaling in peripheral lymphocytes and affected CNS tissues, direct protection of the myelin and suppression of Th1 and Th17 mRNA (Pareek et al., 2011).

3.10.11. Boswellic acids

Boswellic acids can inhibit the release of LTB4 and C4 from intact human PMNLs. These pentacyclic tritepenes can be isolated from the gum resin of *Boswellia serrata*. Daily i.p. administration of the extract of mixed acetylboswellic acids at 20 mg/kg has remarkably decreased the clinical symptoms of EAE in guinea pigs. However, the inflammatory infiltrates in the CNS of treated animals were not significantly less extensive in comparison to the control group. The multiple i.p. administration of boswellic acids could not prevent the ionophore-challenged *ex vivo* release of LTB4 and LTC4 from the PMNLs. Thus, boswellic acids may be considered as *in vitro* potent inhibitors of the LTs biosynthesis (Wildfeuer et al., 1998). Sturner et al. showed that acetyl-11-keto-β-boswellic acid (AKBA) decreases Th17 differentiation *in vitro* and slightly increases Th2 and Treg cells differentiation without a clear effect on Th1 differentiation. Considering the important role of Th17 in the pathogenesis of autoimmune diseases such as MS, AKBA may be a potential therapeutic candidate for this disease (Stürner et al., 2014).

3.10.12. Celastrol

Celastrol was first isolated from *T. wilfordii*, indicating a therapeutic effect in inflammation-related diseases. Intraperitoneal administration of celastrol can attenuate EAE by inhibiting pathogenic Th17 responses (Wang et al., 2015), down-regulating the mRNA expression of IL-17 and IFN-γ, and up-regulating the mRNA expression of IL-4 in the spinal cord (Yang et al., 2017). Optic neuritis which is defined as the inflammation of optic nerve, can be due to the focal inflammation associated with demyelination (Soderstrom, 2001). Celastrol administration can protect the optic nerve by decreasing IFN-γ, TNF-α, IL-1β, and IL-17 expression, increasing IL-4 expression and reducing microgliosis and retinal ganglion cells apoptosis (Yang et al., 2017).

3.11. Saponins

3.11.1. Diosgenin

Diosgenin is extracted from different herbs like *Dioscorea villosa*, *Trigonella foenum-graecum* and *Solanum incanum* (Xiao et al., 2012). It is used as a precursor to synthesize different steroidal drugs in the pharmaceutical industry (Scott et al., 2001). Diosgenin improves OPCs differentiation to mature oligodendrocytes *in vitro* through an estrogen receptor-dependent pathway without any effects on their proliferation, migration and viability (Xiao et al., 2012). An accelerated remyelination in cuprizone-treated mice has also been observed which might be due to its prodifferentiation effects on the OPCs (Xiao et al., 2012).

3.11.2. Periplocoside

Periplocoside A is a pregnane glycoside isolated from the traditional Chinese herbal medicine *Periploca sepium*. It inhibits IL-17 production and Th17 cells differentiation (Zhang et al., 2009). *In vivo* studies indicated that periplocoside E hinders EAE through suppressing IL-12-dependent CCR5 expression and IFN-c-dependent CXCR3 expression in T lymphocytes (Zhu et al., 2006).

3.11.3. Astragaloside IV

Astragaloside IV from the widely used herb, *Astragalus membranaceus* has significantly attenuated the EAE severity. The results of an experiment by He et al. indicated that astragaloside IV is able to suppress the cytokine secretion of Th1 and Th17 from $CD4^+$ cells of EAE mice. Moreover, treating EAE mice with this compound can reduce monocytes infiltration into the anterior median fissure region of the spinal cord and improve demyelination and BBB leakage. All these happen as a result of ROS prevention, pro-inflammatory cytokines reduction, and elevation of p53, iNOS and phosphorylated tau in the CNS (He et al., 2013).

3.12. Cannabinoids

Cannabis sativa has been recognized as a therapeutic agent for centuries. It was used as a muscle relaxant, analgesic and appetite stimulant in the 19th century. In the early 20th century, *Cannabis* was used to ameliorate the symptoms of various diseases like rheumatism and epilepsy. However, the use of this plant as a therapeutic agent decreased due to the abuse possibility and discovery of more effective drugs for the mentioned diseases (Klein, 2005). Recently, there exists an increasing interest for employing cannabinoid-based drugs and different *Cannabis* extracts to control and treat MS symptoms. Some of these preparations are being studied clinically as a result of their promising pharmacological effects. At present, the standardized extract of whole-plant *Cannabis* is in access for clinical research. This is crucial since different phytochemicals (such as cannabidiol and various terpenoids and flavonoids) may have an ameliorative effect or a synergistic activity. Sublingual administration of *Cannabis* medicinal extract (Sativex®) can improve spasm, spasticity and pain in some patients with multiple sclerosis and may help to reduce poor appetite and sleep

Table 1
EAE ameliorative activity of different pure compounds, powders, extracts and essential and fatty oils.

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
Flavonoids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of hesperidin in PBS	Oral administration of hesperidin at 50, 100 and 200 mg/kg/d starting from day 0 for 25 days	Reducing the clinical score at all of the tested doses Reducing the incidence and severity at 100 and 200 mg/kg/day	Haghmorad et al. (2017)
s.c. injection of MOG (35–55)	C57BL/J6 mice	–	Solution of hesperidin in PBS (containing 0.1% CMC)	i.p. administration of hesperidin at 100 mg/kg/d for 7 days starting after 14 days of immunization	Reducing the clinical score of the disease	Ciftci et al. (2015)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of genistein and 7-O-tetradecanoyl-genistein (genestein analog) in PBS	s.c. administration of genestein or its analog at 200 mg/kg/d starting from day 14 p.i. for 7 days	Reducing cell infiltration in the CNS Reducing the clinical signs	Castro et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of genistein in DMSO 4%	Oral administration of genistein at 20 mg/kg/d starting from 21 days before immunization for 42 days	Delaying the disease onset Alleviating severity Reducing the clinical score	Razeghi et al. (2009)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of genistein in DMSO 4%	s.c. administration of genistein at 200 mg/kg/d starting from day 14 p.i. for 7 days	Ameliorating the clinical symptoms	De Paula et al. (2008)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of genistein in DMSO 11%	Oral administration of genistein at 300 mg/kg/d starting on different days (after the appearance of the first clinical signs or day 30 p.i.) for 10 days	Alleviating the severity when administered at the disease onset	Razeghi Jahromi et al. (2014)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Diet supplemented with 0.5% (w/w) naringenin	Oral administration of naringenin-supplemented diet starting on 2 different times for 2 different groups	Reducing the incidence and severity of the disease Attenuating inflammatory infiltration and demyelination in the CNS	Wang et al. (2018a)
s.c. injection of PLP (139–151) peptide	SJL/J mice	–	Solution of baicalin in PBS	i.p. administration of baicalin at 5 and 10 mg/kg/d starting from one day before immunization for 3 days	Decreasing the severity of clinical symptoms and neuroinflammation in the spinal cord	Zeng et al. (2007a)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of baicalin in PBS	i.p. administration of baicalin at 100 mg/kg/d for different groups starting on different days (immunization day or 10 and 15 days p.i.)	Delaying the onset Decreasing the severity Suppressing disease progression	Zhang et al. (2015)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of icariin in 0.5% CMC solution	Oral administration of icariin at 25 mg/kg/d from day 5 until day 15 p.i.	Decreasing the disease score Enhancing clinical recovery Alleviating demyelination	Shen et al. (2015)
Cuprizone feeding	C57BL/6 mice	–	Solution of icariin in 0.5% CMC solution	Oral administration of icariin at 6.25, 12.5 or 25 mg/kg/d for 1 week, after stopping cuprizone treatment	Enhancing remyelination	Zhang et al. (2017)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of icariin in CMC solution	i.g. administration of icariin (at 75, 150 or 300 mg/kg/d) combination with methylprednisolone from 13 days p.i. for 5 days	Ameliorating the neurological signs Reducing the clinical score (at high dose icariin)	Wei et al. (2015)
s.c. injection of gpSCH-MBP	Lewis rats	–	Solution of *epimedium* flavonoids (EF) in saline	i.g. administration of EF at 20 and 60 mg/kg/d starting from day 0 until day 14 p.i.	Delaying the disease onset Reducing the clinical severity	Yin et al. (2012)
Cuprizone feeding	C57BL/6 mice	–	*Epimedium* flavonoids (EF)	i.g. administration of EF at 50 and 100 mg/kg/d starting at the end of week 3 for 21 days or at the end of week 8 for 28 days	Decreasing the extent of demyelination	Liang et al. (2015)
Chalcones						
s.c. injection of MOG (35–55)	C57BL/6 mice	*Glycyrrhiza inflata*	Solution of licochalcone A in saline (containing 5% Tween 80)	Oral treatment with LicoA at 15 and 30 mg/kg/d for 9 days starting from the 10th day p.i.	Reducing the clinical score at 30 mg/kg/d dose	Fontes et al. (2014)
Diarylheptanoids						
Injection of guinea pig MBP (68–86) peptide	Lewis rats	–	Solution of curcumin in 0.5% methylcellulose	Oral administration at 100 or 200 mg/kg/d from days 0–14 p.i.	Reducing the clinical severity Reducing the number of infiltrating inflammatory cells in the spinal cord	Xie et al. (2009)

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Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of curcumin in DMSO	Every other day i.p. administration of curcumin starting from the day of first immunization	Reducing EAE clinical score Reducing IL-17 and IFN-γ expression in the CNS	Kanakasabai et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of curcumin in 0.5% methylcellulose	i.p. administration of curcumin. at 200 mg/kg/d after immunization	Inhibiting apoptosis in the spinal cord in both the acute and chronic stage	Feng et al. (2014)
Lignans						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of arctigenin in DMSO	i.p. administration of arctigenin at 5 or 10 mg/kg/d starting at 2 different times (the test beginning or after the appearance of slight clinical symptoms)	Delaying the clinical symptoms onset Reducing the disease clinical score	Li et al. (2016a)
Stilbenoids						
Cuprizone feeding	C57BL/6 mice	–	Solution of resveratrol in PBS	7 days treatment with a diet containing 0.7% cuprizone following by 3 weeks on 0.2% cuprizone diet plus oral administration of resveratrol at 250 mg/kg/d	Enhancing balance and motor co-ordination Reversing cuprizone-induced demyelination	Ghaiad et al. (2017)
s.c. injection of PLP (139–151)	SJL/J mice	–	Diet supplemented with different concentrations of resveratrol	Oral administration of resveratrol-supplemented diet starting from the EAE induction day	Reducing the disease severity	Imler and Petro (2009)
s.c. injection of PLP (139–151)	SJL/J mice	–	Solution of SRT501 (a formulation of resveratrol) in 2% hydroxypropyl methylcellulose and 0.2% dioctyl sodium sulfosuccinate	Oral administration of SRT501 once in a day at indicated doses and time points	Attenuating neuronal damage in optic nerves Attenuating axonal loss in spinal cord	Shindler et al. (2010)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of SRT501 (a formulation of resveratrol) in 2% hydroxypropyl methylcellulose and 0.2% dioctyl sodium sulfosuccinate Solution of resveratrol in PBS	Oral administration of resveratrol at 100 and 250 mg/kg/d and SRT501 at 250 mg/kg/d for 30 days	Delaying the disease onset by both resveratrol and SRT501 at 250 mg/kg/d Reducing the amount of retinal ganglion cells loss at all of the tested concentrations No prevention or alteration in the phenotype of inflammation in the spinal cords or optic nerves	Fonseca-Kelly et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Diet supplemented with resveratrol	Oral administration of resveratrol-supplemented diet (20 mg/kg/d of resveratrol) for 3 different groups starting at different times	Exacerbating the clinical and histological signs	Sato et al. (2013)
Naphtoquinones						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of plumbagin in DMSO	i.p. administration of plumbagin at 2 mg/kg/d starting from 2 different times (3 days before immunization or day 7 p.i.)	Reducing EAE score, inflammation and demyelination in the spinal cord	Jia et al. (2011)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of plumbagin in PBS	i.p. administration of plumbagin at 2 mg/kg/d starting from 3 days before immunization until day 15 p.i.	Alleviating the clinical symptoms Ameliorating spinal cord inflammation and demyelination	Zhang et al. (2014b)
Phenolic acids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of salvianolic acid B in PBS	i.p. administration of salvianolic acid B at 30 mg/kg from day 12 p.i. for 14 days	Reducing the disease severity and inflammatory cells infiltration into the CNS Inhibiting Th1 cells responses	Dong et al. (2016)
Intradermal administration of guinea pig MBP	Wistar rats	–	Solution of caffeic acid phenethyl ester (CAPE) (50 μmol/mL) (one of the active components of honey propolis)	i.p. injection of CAPE at 25 μmol/kg/d starting from day 1 until day 14 p.i	Reducing the clinical severity, inflammatory infiltration and glial activation/proliferation	Ilhan et al. (2004)
Glucosinolates						
s.c. injection of MOG (35–55)	C57BL/6 mice	*Moringa oleifera*	Solution of glucomoringin (GMG) in PBS + 5 μl/mouse myrosinase enzyme (resulting in GMG isothiocyanate (GMG-ITC) generation)	Daily i.p. administration of GMG-ITC (10 mg/kg GMG + 5 μl/mouse myrosinase) from 1 week before EAE induction until 21st day p.i.	Reducing demyelination, axonal loss and reactive species generation Protecting the CNS tissue	Galuppo et al. (2014)

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Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
s.c. injection of MOG (35–55)	C57BL/6 mice	*Moringa oleifera*	Solution of glucomoringin (GMG) in PBS + 5 μl/mouse myrosinase enzyme (resulting in GMG isothiocyanate (GMG-ITC) generation)	Daily i.p. administration of GMG-ITC (10 mg/kg GMG + 5 μl/mouse myrosinase) from 1 week before EAE induction until 28th day p.i.	Reducing the disease incidence, severity and progression Enhancing neurological functions recovery	Giacoppo et al. (2016)
Coumarins						
s.c. injection of MOG (35–55)	C57 BL/6 mice	–	Solution of osthole in N,N-dimethylformamide, tween and 0.9% sodium chloride (1:1:8)	i.p. administration of osthole at 30 mg/kg twice daily for 2 days, then 15 mg/kg twice daily thereafter, starting from day 7 or day 13 p.i.	Ameliorating the clinical severity Stabilizing neurological deficits Delaying the disease onset	Chen et al. (2010)
Sesquiterpene alkaloids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of huperzine A in PBS	i.p. administration of huperzine A at 0.05 and 0.2 mg/kg/d starting from day 0 or day 10 p.i.	Reducing demyelination and infiltration in the spinal cord Ameliorating EAE symptoms Reducing severity when administered at 0.2 mg/kg/d	Wang et al. (2012)
Quinolizidine alkaloids						
s.c. injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in saline	i.p. administration of matrine at 150 and 200 mg/kg/d from day 1 until day 16 p.i.	Delaying the disease onset Reducing the clinical score and CNS inflammation and demyelination	Zhao et al. (2011)
s.c. injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in PBS	i.p. administration of matrine solution at 150, 200 and 250 mg/kg/d from day 1 until day 17 p.i.	Delaying the disease onset Reducing the clinical score and CNS inflammation and demyelination	Kan et al. (2013)
s.c. injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in saline	i.p. administration of matrine solution at 200 mg/kg/d from day 1 until day 17 p.i.	Delaying the disease progression Lowering the clinical score and body weight loss	Kan et al. (2014)
s.c. injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in saline	i.p. administration of matrine at 150 and 250 mg/kg/d from day 1 until day 17 p.i.	Alleviating the disease severity Lowering the clinical score and body weight loss	Zhang et al. (2013)
s.c. injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in saline	i.p. administration of matrine at 150 and 250 mg/kg/d from day 1 until day 17 p.i.	Delaying the disease onset Alleviating the clinical severity Preventing body weight loss	Zhu et al. (2016)
Intradermal injection of gpSCH-CFA emulsion	Wistar rats	–	Solution of matrine in saline	i.p. administration of matrine at 200 mg/kg/d from days 1–16 p.i.	Reducing the clinical score and body weight loss Inhibiting inflammatory infiltration	Kan et al. (2015)
Benzyl tetrahydroisoquinoline alkaloids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of berberine in PBS	i.g. administration at 30 mg/kg/d starting at the disease onset until day 35 p.i.	Reducing inflammatory cells infiltration Ameliorating demyelination in the lumbar spinal cord	Ma et al. (2010)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of berberine in ddH_2O	i.g. administration of berberin at 200 mg/kg/d for 2 different groups starting on different days (3 days before or 9 days after immunization onwards)	Improving clinical score and spinal cord histopathology Reducing the disease severity as well as inflammation and demyelination in the spinal cord	Qin et al. (2010)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of berberine in PBS	i.g. administration at 30 mg/kg/d starting at the disease onset until day 35 p.i.	Protection against neuronal damage via reducing laminin degradation and inhibiting gelatinase activity	Jiang et al. (2013)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of berbamine in DMSO	i.p. administration of berbamin at 50 mg/kg/d for 2 different groups starting on different days (day 7 or day 10 p.i. onwards)	Reducing demyelination and inflammation in the spinal cord lesions of treated mice	Ren et al. (2008)
s.c. injection of MBP(68–82) emulsion	Lewis rats	–	Solution of sinomenine in PBS	i.p. administration of sinomenine at 50, 100 or 200 mg/kg/d from day (−1) to day 3 p.i.	Reducing EAE clinical score Delaying the disease progression	Zeng et al. (2007b)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of sinomenine or sinomenine synthetic derivative in PBS	i.p. administration of sinomenine or its derivative at 15 mg/kg/d from days 1–28	Reducing EAE score by both compounds	Yan et al. (2010)
Monoterpenoids						

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Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
s.c. injection of guinea pig MBP in the hind footpads	Lewis rats	*Cornus officinalis*	Solution of cornel iridoid glycoside (CIG) in saline	i.g. administration of CIG at 30, 60 and 120 mg/kg/d starting from day 0 until day 20 p.i.	Reducing the clinical score and severity of neurological deficits Delaying the disease onset Preventing body weight loss	Yin et al. (2014)
s.c. injection of MOG (35–55)	C57BL/6 J mice	*Cornus officinalis*	Solution of CIG in saline	i.g. administration of CIG at 25, 50 and 100 mg/kg/d from days 0–32 p.i.	Delaying the disease onset (at all doses) Reducing the clinical score (at 50 and 100 mg/kg)	Qu et al. (2016)
s.c. injection of MOG (35–55)	C57BL/6 mice	-	Solution of carvacrol in PBS (containing 2% Tween 80)	Every other day i.p. administration of carvacrol at 5 and 10 mg/kg from day 0–21 p.i.	Reducing EAE clinical score, inflammatory infiltration and IFN-γ and IL-6 production Enhancing IL-4, IL-10 and TGF-β levels	Mahmoodi et al. (2019a)
Sesquiterpenoids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of β-elemene in saline	Every other day i.p. administration of β-elemene at 20 mg/kg starting from day 1 until day 11 or day 15 p.i.	Reducing the clinical severity, inflammatory cells infiltration and axonal damage Delaying the disease onset	Zhang et al. (2011)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	SM933 (a derivative of artemisinin)	i.p. administration of SM933 at 400 μg/per mouse/d starting at 2 different times (3 days before immunization or day 8 p.i.) onwards	Reducing EAE severity and demyelination of the spinal cord	Wang et al. (2007)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	SM934 (a derivative of artemisinin)	Oral administration of SM934 at 10 mg/kg/d starting at different times (day 1, day 11 or day 18 p.i.) until day 30 p.i.	Ameliorating EAE via suppressing Th1 and Th17 responses Increasing Treg cells expansion and differentiation	Li et al. (2013)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of β-caryophyllene in saline (containing 5% tween 80)	Oral administration of β-caryophyllene at 25 and 50 mg/kg/d from day 10–19 p.i.	Reducing the clinical score, disease severity and inflammatory infiltration into the CNS Preventing H_2O_2, NO, IFN-γ, TNF-α and, IL-17 production	Fontes et al. (2017)
Diterpenoids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of LLDT-8 (a derivative of triptolide) in PBS (containing 2% propanediol)	i.p. administration of LLDT-8 at 1 mg/kg/d starting from the immunization day until day 18 p.i.	Reducing EAE incidence and severity Preventing body weight loss	Fu et al. (2006)
s.c. injection of PLP (139–151)	SJL/J mice	*Tripterygium wilfordii*	Triptolide or *T.wilfordii* extract in corn oil	Oral administration of triptolide or *T.wilfordii* extract (at 100 μg/kg/d or 37.5 mg/kg/d, respectively) starting at 2 different times (day 0 or day 10) until day 25 p.i.	Ameliorating EAE Suppressing relapses	Kizelsztein et al. (2009)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of triptolide in PBS	i.p. administration of triptolide at 100 μg/kg/d starting from the immunization day for 28 days	Delaying the disease onset Reducing the severity Suppressing inflammatory cells infiltration in the CNS	Wang et al. (2008)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of andrographolide in PBS	i.p. administration of andrographolide at 4 mg/kg/d starting from 1 week before immunization	Regulating immune responses Reducing the severity	Iruretagoyena et al. (2005)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of kirenol in distilled water	Oral administration of kirenol at 2 mg/kg/d from days 0–25	Delaying the clinical onset and peak clinical disease Reducing CNS demyelination during EAE	Xiao et al. (2015)

(*continued on next page*)

Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
s.c. injection of MOG (35–55)	C57BL/6 mice (acute phase)	–	Solution of carnosol in PBS	i.p. administration of carnosol at 50 mg/kg/d from day 0–30 p.i.	Delaying the disease onset Reducing demyelination, severity and inflammatory infiltration into the CNS	Li et al. (2018)
	C57BL/6 mice (chronic phase)			i.p. administration of carnosol at 50 mg/kg/d from day 25–60 p.i.	Reducing the clinical score, demyelination and neurological damage	
Triterpenoids						
Bilateral tail base injection with MOG (35–55)	C57BL/J6 mice	*Olea europaea*	Solution of oleanolic acid in PBS	i.p. administartion of oleanolic acid at 50 mg/kg/d for 2 different groups starting from day 7 or day 12 p.i. until days 21–24 p.i.	Reducing blood–brain barrier leakage and inflammatory cells infiltration within the CNS Inhibiting proinflammatory cytokines and chemokines Stimulating anti-inflammatory cytokines	Martin et al. (2010)
s.c. injection of MOG (35–55)	C57BL/J6 mice	–	Solution of oleanolic acid or erythrodiol in PBS	i.p. administration of oleanolic acid or erythrodiol at 50 mg/kg/d starting at different times (7 days before immunization, immunization day or day 12 p.i.)	Delaying the disease onset Reducing the severity	Martin et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of CDDO-Me, CDDO-EA and CDDO-TFEA (three derivatives of oleanolic acid) in PBS (containing tween-80)	Five i.p. administrations of each compound every 48 h starting after 15 days of immunization	Improving survival and abrogating clinical symptoms within the first two weeks of treatment	Pareek et al. (2011)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of euphol in saline (containing 5% tween 80)	Oral administration of euphol at 1,3 and 10 mg/kg/d from days 0–25 p.i. or 10 mg/kg/d from days 15–25 p.i.	Significant blocking of the clinical manifestations Inhibiting locomotor deficits Protecting against weight loss by 10 mg/kg dose	Dutra et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of celastrol in DMSO	i.p. administration of celastrol on days 1, 3, 5 and 7 p.i.	Delaying the disease onset Reducing inflammatory infiltration into the spinal cord Inhibiting the immune response in the peripheral lymphoid tissues	Wang et al. (2015)
Injection of MBP	Sprague Dawley rats	–	Solution of celastrol in 1% DMSO	i.p. administration of celastrol at 1 and 2 mg/kg/d from day 0–13 p.i.	Ameliorating the disease severity and inflammatory infiltration Protecting the optic nerve and reducing microgliosis and retinal ganglion cells apoptosis	Yang et al. (2017)
Steroidal saponins						
Cuprizone feeding	C57BL/6 J mice	–	Solution of diosgenin in corn oil	Every other day i.p. injection of diosgenin at 20 mg/kg starting from week 7 until the end of week 8 p.i.	Accelerating and enhancing remyelination Increasing the number of mature oligodendrocytes in the corpus callosum	Xiao et al. (2012)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Periploca sepium*	Solution of periplocoside A in PBS (containing 5% surfactant and 0.2% DMSO)	Oral administration of periplocoside A at 25 and 50 mg/kg starting from the immunization day and continuing throughout the study	Reducing the incidence and severity Preventing body weight loss	Zhang et al. (2009)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of periplocoside E in PBS (containing 1.6% ethanol)	i.p. administration of periplocoside E at 10 mg/kg/d starting from the day of immunization and continuing throughout the study	Reducing the incidence and severity Preventing body weight loss	Zhu et al. (2006)
Cycloartane triterpene saponin						

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Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Astragaloside IV	i.p. administration of astragaloside IV at 20 mg/kg/d from the day before immunization for 2 weeks	Preventing EAE aggravation through inhibiting ROS generation and increasing anti-oxidative capability of neuronal cells	He et al. (2013)
Cannabinoids						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of cannabidiol in PBS (containing cremophor and EtOH)	i.p. administration of cannabidiol at 5 mg/kg on days 19, 20 and 21 p.i.	Reducing the clinical score Ameliorating the clinical signs during the days of injections Delaying the disease progression	Kozela et al. (2011)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Cannabis sativa*	Solution of cannabidiol in saline (containing EtOH and tween 20)	i.p. administration of cannabidiol at 10 mg/kg/d starting after the occurrence of first clinical signs until day 28 p.i.	Reducing body weight loss and EAE clinical score	Giacoppo et al. (2015a)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Cannabis sativa*	1% cannabidiol cream	Every day topical administration of 1% cannabidiol cream to the lower limbs starting from the onset of disease signs until sacrifice	Reducing the clinical score, demyelination and axonal loss Increasing response to mechanical stimulus	Giacoppo et al. (2015b)
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of HU-210 (a tetrahydro cannabinol derivative) in PBS	Every other day i.p. administration of HU-210 at 3, 10 and 30 mg/kg starting from day 1 until day 17	Ameliorating the severity of clinical signs at 30 mg/kg Reducing the IL-12, TNFα and IFN-γ levels at 30 mg/kg Improving the balance beam score at all of the tested doses	Aarabi et al. (2011)
Other compounds						
s.c. injection of MOG (35–55)	C57BL/6 mice	–	Solution of embelin in PBS	Oral administration of embelin at 25 and 50 mg/kg/d starting from days 0–24 p.i.	Reducing inflammatory cells in the white matter of the lumbar spinal cord Reducing EAE clinical score and CNS demyelination	Xue et al. (2014)
Powders						
s.c. injection of MOG (35–55)	Wistar rats	*Nigella sativa*	Suspension of *Nigella sativa* seeds powder in distilled water	Oral administration at 2.8 g/kg/d for different groups starting at different times (2 weeks prior to EAE induction or after the appearance of first clinical signs) until the end of the experiment	Ameliorating EAE clinical manifestations Reducing the severity	Fahmy et al. (2014)
s.c. injection of MOG (35–55)	Wistar rats	*Nigella sativa*	Suspension of *Nigella sativa* seeds powder in distilled water	Oral administration at 2.8 g/kg/d for different groups starting at different times (2 weeks prior to EAE induction or after the appearance of first clinical signs) until the end of the experiment	Suppressing meningeal inflammatory cells infiltration Increasing remyelination in the cerebellum	Noor et al. (2015)
s.c. injection of MOG (35–55)	Chronic form of EAE in C57BL/6 mice	*Vaccinium ashei*	Freeze-dried blueberry powder	1% freeze-dried blueberry supplemented diet starting from 3 days before the immunization protocol until the end of the experiment	Reducing the disease incidence and severity of relapses Suppressing demyelination	Xin et al. (2012)
Immunization with PLP peptide (139–151) (Anaspec)	Relapsing – remitting form of EAE in SJL mice			1% freeze-dried blueberry supplemented diet starting on day 39 (after the first relapse-remission cycle) until the end of the experiment	Attenuating clinical severity	
Extracts						
s.c. injection of MOG (35–55)	C57BL/6 mice	*Achillea millefolium*	Solution of aerial parts aqueous extract in distilled water	Administration of aqueous extract at 1, 5, and 10 mg/mouse/d starting from day 1 p.i. for 21 days	Attenuating disease severity, demyelinating lesions and inflammatory responses	Vazirinejad et al. (2014)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Crocus sativus*	Suspension of EtOH (80%) extract in double distilled water (DDW)	Oral gavage of saffron extract at 500 mg/kg/d starting on the day of immunization	Delaying the disease onset Reducing clinical score Preventing oxidative stress and leukocyte infiltration to the CNS	Ghazavi et al. (2009)

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Table 1 (*continued*)

EAE induction method	Experimental animal	Plant spp.	Active constituent/preparation	Dosing	Result	Ref.
Intradermal administration of SCH-CFA.(rat spinal cord homogenate- complete Freund's adjuvant)	Dark Agouti rats	–	Solution of standardized dry olive leaf extract (DOLE) (EFLA®943) in water	i.g. administration of DOLE at 80 mg/kg/d starting on the day of immunization	Decreasing cumulative disease index, disease duration and IFN-γ and IL-17 production	Miljkovic et al. (2009)
Intradermal injection of MOG (35–55)	C57BL/6 mice	*Hymenaea courbaril*	Solution of EtOH extract in 1% EtOH	Every other day i.p. administration of extract at 0.4 and 1 mg/mouse to different groups starting on different days according to the proposed test	Retarding the disease development Reducing the clinical score	Miyake et al. (2006)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Zingiber officinale*	Solution of ginger extract in PBS	Every other day i.p. administration of ginger extract at 200 and 300 mg/kg from day 3 until day 30 p.i.	Reducing the disease severity, body weight loss and CNS inflammation	Jafarzadeh et al. (2014)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Clerodendrum splendens*	Solution of a polysaccharide fraction from the plant leaves in the PBS	i.p. administration at 50 mg/kg/d starting from day 4 p.i.	Delaying the disease onset Reducing the EAE clinical severity	Kouakou et al. (2013)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Helleborus purpurascens*	MCS-18 (a natural product from the roots of *Helleborus purpurascens*)	i.p. administration of MCS-18 (100 μg) on days −1, 1 and 3 Oral administration of MCS-18 for different groups starting at different times	Reducing the paralysis Demonstrating long-lasting immunosuppressive effects	Horstmann et al. (2008)
s.c. injection of MOG (35–55)	C57BL/6 mice	*Thymus vulgaris*	Solution of ethanol extract in PBS	Every other day i.p. administration of extract at 50 and 100 mg/kg from day 0–21 p.i.	Reducing the clinical symptoms, CNS histopathological scores and IFN-γ and IL-6 production by splenocytes Increasing IL-10 and TGF-β production	Mahmoodi et al. (2019b)
Essential oils						
s.c. injection of MOG (35–55)	C57BL/6 mice	*Copaifera officinalis*	Copaiba oil in saline (containing 5% tween 80)	Obtaining the mice splenocytes on day 20 p.i. and treating them with copaiba oil at 25, 50 and 100 μg/mL	Inhibiting NO and H_2O_2 production (at 100 μg/mL) Reducing TNF-α, IFN-γ and IL-17 (at 50 and 100 μg/mL)	Dias et al. (2014)
Fatty oils						
s.c. injection of MOG (92–106)	SJL mice (acute phase)	*Borago officinalis*	Ultra-refined omega-6 fatty acid-rich lipid (Roche company	Oral administration of 250–300 μL/d starting from day 7 p.i. until day 13 or 21	Inhibiting the clinical incidence and histological manifestations of acute EAE	Harbige et al. (2000)
	SJL mice (relapse phase)			Oral administration of 250–300 μL/d starting from days 25–45	Inhibiting the clinical relapse phase of chronic relapsing EAE	
s.c. injection of MOG (35–55)	C57BL/6 mice	*Sesamum indicum*	Solution of sesame oil in PBS	i.p. administration of sesame oil (4 mL/kg/d) starting on day 3 before the immunization until day 25 p.i.	Reducing the clinical symptoms and leukocytes infiltration into the brain	Mosayebi et al. (2007)

(Wade et al., 2003, 2004). Also, delta-9-tetrahydrocannabinol as an active constituent of *Cannabis*, was shown to improve the ratings of spasticity in 13 patients with MS at doses greater than 7.5 mg (Ungerleider et al., 1987). It is believed that cannabidiol may regulate the unwanted effects of tetrahydocannabinol (McPartland and Russo, 2001); however, the MS amending effects of cannabidiol as an important phytochemical present in the *Cannabis* extract has not been investigated in clinical studies.

3.12.1. Cannabidiol

Cannabidiol is a non-psychoactive cannabinoid compound (Fig. 5) and the major *Cannabis*-derived non-CB_1/CB_2 receptor ligand (Showalter et al., 1996) with immunomodulatory activities (Kozela et al., 2011). Systemic administration of cannabidiol during the EAE onset ameliorates the clinical signs and delays the disease progression. Moreover, treated mice have lesser axonal damage, weaker inflammation and fewer $CD3^+$ infiltrates in their spinal cord (Kozela et al., 2011). Cannabidiol is able to inhibit FAS pathway activation, reduce cleaved-caspase 3 expression levels, prevent mitochondrial permeability alteration and thus, results in the absence of apobody formation in the spinal cord of treated EAE mice (Giacoppo et al., 2015a). Interestingly, topical treatment with cannabidiol cream reduces the clinical score, demyelination and axonal loss in the spinal cord. Cannabidiol confronts the EAE-induced damage by decreasing the release of CD4 and CD8α T cells and the expression of various direct or indirect markers of inflammation including p-selectin, GFAP, TGF-β, Foxp3, TNF-α, and IFN-γ (Giacoppo et al., 2015b).

3.12.2. HU-210 (1,1-dimethylheptyl-11-hydroxytetrahydrocannabinol)

Aarabi et al. have shown the ameliorative effect of HU-210 (Fig. 5)-a CB_1 receptor ligand-on EAE. This compound has reduced the clinical score as well as the serum levels of TNF-α and IL-12 and increased the serum level of IL-4 as an anti-inflammatory cytokine (Aarabi et al., 2011).

3.13. Powders, extracts and oils

Various plants powders including *Nigella sativa* (Fahmy et al., 2014; Noor et al., 2015) and *Vaccinium ashei* (Xin et al., 2012), extracts including *Achillea millefolium* (Vazirinejad et al., 2014), *Crocus sativus* (Ghazavi et al., 2009), *Olea europaea* (Miljkovic et al., 2009), *Hymenaea courbaril* (Miyake et al., 2006), *Zingiber officinale* (Jafarzadeh et al., 2014), *Clerodendrum splendens* (Kouakou et al., 2013), *Helleborus purpurascens* (Horstmann et al., 2008) and *Thymus vulgaris* (Mahmoodi et al., 2019b), essential oils such as copaiba oil (Dias et al., 2014) and fatty oils like omega-6 fatty acid-rich lipid (Harbige et al., 2000) or sesame oil (Mosayebi et al., 2007) have represented different levels of EAE improvement. Table 1 summarizes the study design and EAE ameliorative effects of natural products in animal studies.

5. Discussion and conclusion

Bioactive natural products have opened new horizons in treating some neurodegenerative diseases as a result of their efficacy, multi-mechanistic modes of action and potential safety. This review article has illustrated the potency of some natural products in alleviating EAE symptoms as an animal model for MS. Literature data review showed that natural products can improve EAE symptoms through different mechanisms like reducing the oxidative stress, decreasing demyelination and inflammation in the CNS, protecting the BBB, and enhancing remyelination.

The anti-inflammatory effects are usually due to decreasing proinflammatory and inflammatory cytokines, up-regulating anti-inflammatory factors and suppressing the infiltration into the CNS. NF-κB is among the master regulatory transcription factors that control the activity of inflammatory cells including macrophages, T cells and microglia (Cramer et al., 2014). Its activation in inflammatory cells, including microglia/macrophages and T cells leads to inflammation and EAE development. In contrast, NF-κB activation in neurons and oligodendrocytes protects them against inflammation (Yue et al., 2018). Data review indicated that cornel iridoid glycosides, artemisinin, triptolide and andrographolide can inhibit the activation of this factor and as a result possess strong anti-inflammatory activity. Matrine, icariin, berberine, and astragaloside IV improve the BBB integrity which is another important mechanism in EAE attenuation because it can suppress B cells, monocytes and macrophages to enter the CNS and lowers inflammation. Moreover, the clinical severity of MS is related to the degree of BBB disruption (Cramer et al., 2014).

Currently, there are two natural-isolated drugs present in the market for treating MS symptoms, Gilenya® and Sativex®. The development of Gilenya® (fingolimod) happened by investigating the active sites of natural immunosuppressive molecule, myriocin. Replacing the lipophilic side chain with a straight alkane, simplification of the chiral head group (Fujita et al., 1994, 1995) and introducing a 1,4-phenylene group to influence the pharmacological and physicochemical properties of acyclic analogues resulted in fingolimod discovery (Adachi et al., 1995; Fujita et al., 1996). Different classes of natural products have shown EAE ameliorative properties and studying the active part of each molecule can result in the formation of a complete library of lead compounds for further research.

Sativex® is another medicine that has been developed for treating MS symptoms. This *Cannabis*-based oromucosal spray that helps to cure the spasticity and neuropathic pain of MS patients contains the cannabidiol and tetrahydrocannabinol extracts of *Cannabis sativa*. There exists an abuse potential during Sativex® use since an investigation has indicated some abuse liability in cannabis smokers compared to the placebo at higher doses; yet, the obtained scores were lower than the equivalent doses of tetrahydrocannabinol. As a result, it was suggested that the abuse or dependence potential of Sativex® may probably happen in only a few recipients (Robson, 2011). Among the different anti-MS natural products isolated from *Cannabis* spp, a special attention should be paid to cannabidiol because this compound is non-psychoactive and is able to reduce the disease severity and demyelination even in the topical form. Therefore, it is worth considering cannabidiol as a potential candidate for subsequent animal and clinical studies.

Further research is necessary to understand the detailed neuroprotective mechanisms of natural products, their optimal dose, and correct consumption since the dose or the rout of drug administration can change the drug action. Thus, investigating these factors on EAE ameliorative efficacy is highly encouraged. Taken together, the use of natural products as promising potential therapeutic agents for treating MS is of great value and worth profound SAR, animal and clinical studies.

Conflicts of interest

There is no conflict of interest.

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References

Aarabi, M., Shahaboddin, M., Parastouei, K., Motallebi, M., Jafarnejad, A., Mirhashemi, M., et al., 2011. Evaluation of 11-hydroxy-Δ8-THC-dimethylheptyl effects on cytokines profile and locomotor tests in experimental autoimmune encephalomyelitis. J. Med. Plants Res. 5 (17), 4244–4250.

Adachi, K., Kohara, T., Nakao, N., Arita, M., Chiba, K., Mishina, T., et al., 1995. Design, synthesis, and structure-activity relationships of 2-substituted-2-amino-1,3-

propanediols: discovery of a novel immunosuppressant, FTY720. Bioorg. Med. Chem. Lett 5 (8), 853–856.
Assis, L.C., Straliotto, M.R., Engel, D., Hort, M.A., Dutra, R.C., de Bem, A.F., 2014. β-Caryophyllene protects the C6 glioma cells against glutamate-induced excitotoxicity through the Nrf2 pathway. Neuroscience 279, 220–231.
Babbe, H., Roers, A., Waisman, A., Lassmann, H., Goebels, N., Hohlfeld, R., et al., 2000. Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. J. Exp. Med. 192 (3), 393–404.
Barfod, L., Kemp, K., Hansen, M., Kharazmi, A., 2002. Chalcones from Chinese liquorice inhibit proliferation of T cells and production of cytokines. Int. Immunopharmacol. 2 (4), 545–555.
Becher, B., Durell, B.G., Noelle, R.J., 2002. Experimental autoimmune encephalitis and inflammation in the absence of interleukin-12. J. Clin. Investig. 110 (4), 493–497.
Calabrese, C., Berman, S.H., Babish, J.G., Ma, X., Shinto, L., Dorr, M., et al., 2000. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res. 14 (5), 333–338.
Castro, S.B., Junior, C.O., Alves, C.C., Dias, A.T., Alves, L.L., Mazzoccoli, L., et al., 2012. Immunomodulatory effects and improved prognosis of experimental autoimmune encephalomyelitis after O-tetradecanoyl-genistein treatment. Int. Immunopharmacol. 12 (2), 465–470.
Chen, X., Pi, R., Zou, Y., Liu, M., Ma, X., Jiang, Y., et al., 2010. Attenuation of experimental autoimmune encephalomyelitis in C57BL/6 mice by osthole, a natural coumarin. Eur. J. Pharmacol. 629 (1), 40–46.
Cheng, H., Xia, B., Zhang, L., Zhou, F., Zhang, Y.X., Ye, M., et al., 2006. Matrine improves 2,4,6-trinitrobenzene sulfonic acid-induced colitis in mice. Pharmacol. Res. 53 (3), 202–208.
Chitnis, T., Khoury, S.J., 2003. Cytokine shifts and tolerance in experimental autoimmune encephalomyelitis. Immunol. Res. 28 (3), 223–239.
Chu, X., Ci, X., Wei, M., Yang, X., Cao, Q., Guan, M., et al., 2012. Licochalcone A inhibits lipopolysaccharide-induced inflammatory response *in vitro* and *in vivo*. J. Agric. Food Chem. 60 (15), 3947–3954.
Ciftci, O., Ozcan, C., Kamisli, O., Cetin, A., Basak, N., Aytac, B., 2015. Hesperidin, a *Citrus* flavonoid, has the ameliorative effects against experimental autoimmune encephalomyelitis (EAE) in a C57BL/J6 mouse model. Neurochem. Res. 40 (6), 1111–1120.
Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372 (9648), 1502–1517.
Constantinescu, C.S., Farooqi, N., O'Brien, K., Gran, B., 2011. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br. J. Pharmacol. 164 (4), 1079–1106.
Copmans, D., Orellana-Paucar, A.M., Steurs, G., Zhang, Y., Ny, A., Foubert, K., et al., 2017. Methylated flavonoids as anti-seizure agents: naringenin 4',7-dimethyl ether attenuates epileptic seizures in zebrafish and mouse models. Neurochem. Int. 112, 124–133.
Cramer, S.P., Simonsen, H., Frederiksen, J.L., Rostrup, E., Larsson, H.B., 2014. Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI. Neuroimage Clin. 4, 182–189.
de las Heras, B., Hortelano, S., 2009. Molecular basis of the anti-inflammatory effects of terpenoids. Inflamm. Allergy - Drug Targets 8 (1), 28–39.
De Paula, M.L., Rodrigues, D.H., Teixeira, H.C., Barsante, M.M., Souza, M.A., Ferreira, A.P., 2008. Genistein down-modulates pro-inflammatory cytokines and reverses clinical signs of experimental autoimmune encephalomyelitis. Int. Immunopharmacol. 8 (9), 1291–1297.
Dey, A., Mukherjee, A., 2018. Plant-derived alkaloids: a promising window for neuroprotective drug discovery. In: Brahmachari, G. (Ed.), Discovery and Development of Neuroprotective Agents from Natural Products. Elsevier, pp. 237–320.
Dheen, S.T., Kaur, C., Ling, E.A., 2007. Microglial activation and its implications in the brain diseases. Curr. Med. Chem. 14 (11), 1189–1197.
Dias, D.S., Fontes, L.B., Crotti, A.E., Aarestrup, B.J., Aarestrup, F.M., da Silva Filho, A.A., et al., 2014. Copaiba oil suppresses inflammatory cytokines in splenocytes of C57Bl/6 mice induced with experimental autoimmune encephalomyelitis (EAE). Molecules 19 (8), 12814–12826.
Dong, Z., Ma, D., Gong, Y., Yu, T., Yao, G., 2016. Salvianolic acid B ameliorates CNS autoimmunity by suppressing Th1 responses. Neurosci. Lett. 619, 92–99.
Dutra, R.C., de Souza, P.R., Bento, A.F., Marcon, R., Bicca, M.A., Pianowski, L.F., et al., 2012. Euphol prevents experimental autoimmune encephalomyelitis in mice: evidence for the underlying mechanisms. Biochem. Pharmacol. 83 (4), 531–542.
Dvorakova, M., Landa, P., 2017. Anti-inflammatory activity of natural stilbenoids: a review. Pharmacol. Res. 124, 126–145.
Ellwardt, E., Zipp, F., 2014. Molecular mechanisms linking neuroinflammation and neurodegeneration in MS. Exp. Neurol. 262, 8–17.
Emami, S.A., Sahebkar, A., Javadi, B., 2016. Paresthesia: a review of its definition, etiology and treatments in view of the traditional medicine. Curr. Pharmaceut. Des. 22 (3), 321–327.
Esmaeil, N., Anaraki, S.B., Gharagozloo, M., Moayedi, B., 2017. Silymarin impacts on immune system as an immunomodulator: one key for many locks. Int. Immunopharmacol. 50, 194–201.
Fahmy, H.M., Noor, N.A., Mohammed, F.F., Elsayed, A.A., Radwan, N.M., 2014. *Nigella sativa* as an anti-inflammatory and promising remyelinating agent in the cortex and hippocampus of experimental autoimmune encephalomyelitis-induced rats. J. Basic Appl. Zool. 67 (5), 182–195.
Feng, J., Tao, T., Yan, W., Chen, C.S., Qin, X., 2014. Curcumin inhibits mitochondrial injury and apoptosis from the early stage in EAE mice. Oxid. Med. Cell. Longev. 2014, 728–751.
Fletcher, J.M., Lalor, S.J., Sweeney, C.M., Tubridy, N., Mills, K.H., 2010. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin. Exp. Immunol. 162 (1), 1–11.
Fonseca-Kelly, Z., Nassrallah, M., Uribe, J., Khan, R.S., Dine, K., Dutt, M., et al., 2012. Resveratrol neuroprotection in a chronic mouse model of multiple sclerosis. Front. Neurol. 3, 84.
Fontes, L.B., Dos Santos Dias, D., de Carvalho, L.S., Mesquita, H.L., da Silva Reis, L., Dias, A.T., et al., 2014. Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. J. Pharm. Pharmacol. 66 (6), 886–894.
Fontes, L.B.A., Dias, D.D.S., Aarestrup, B.J.V., Aarestrup, F.M., Da Silva Filho, A.A., Correa, J., 2017. β-Caryophyllene ameliorates the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. Biomed. Pharmacother. 91, 257–264.
Fu, N.W., 1984. Antitumor effect and pharmacological actions of beta-elemene isolated from the rhizome of *Curcuma aromatica*. Zhongyao Tongbao 9 (2), 83–87.
Fu, Y.F., Zhu, Y.N., Ni, J., Zhong, X.G., Tang, W., Zhou, R., et al., 2006. 5R)-5-hydroxytriptolide (LLDT-8), a novel triptolide derivative, prevents experimental autoimmune encephalomyelitis via inhibiting T cell activation. J. Neuroimmunol. 175 (1–2), 142–151.
Fujita, T., Inoue, K., Yamamoto, S., Ikumoto, T., Sasaki, S., Toyama, R., et al., 1994. Potent immunosuppressant, 14-deoxomyriocin, (2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-hydroxymethyleicos-6-enoic acid and structure-activity relationships of myriocin derivatives. J. Antibiot. (Tokyo) 47, 216–224.
Fujita, T., Yoneta, M., Hirose, R., Sasaki, S., Inoue, K., Kiuchi, M., et al., 1995. Simple compounds, 2-alkyl-2-amino-1,3-propanediols have potent immunosuppressive activity. Bioorg. Med. Chem. Lett 5 (8), 847–852.
Fujita, T., Hirose, R., Yoneta, M., Sasaki, S., Inoue, K., Kiuchi, M., et al., 1996. Potent immunosuppressants, 2-Alkyl-2-aminopropane-1,3-diols. J. Med. Chem. 39 (22), 4451–4459.
Funakoshi-Tago, M., Tago, K., Nishizawa, C., Takahashi, K., Mashino, T., Iwata, S., et al., 2008. Licochalcone A is a potent inhibitor of TEL-Jak2-mediated transformation through the specific inhibition of Stat3 activation. Biochem. Pharmacol. 76 (12), 1681–1693.
Furusawa, J., Funakoshi-Tago, M., Tago, K., Mashino, T., Inoue, H., Sonoda, Y., et al., 2009. Licochalcone A significantly suppresses LPS signaling pathway through the inhibition of NF-κB p65 phosphorylation at serine 276. Cell. Signal. 21 (5), 778–785.
Galazka, G., Stasiolek, M., Walczak, A., Jurewicz, A., Zylicz, A., Brosnan, C.F., et al., 2006. Brain-derived heat shock protein 70-peptide complexes induce NK cell-dependent tolerance to experimental autoimmune encephalomyelitis. J. Immunol. 176 (3), 1588–1599.
Galuppo, M., Giacoppo, S., De Nicola, G.R., Iori, R., Navarra, M., Lombardo, G.E., et al., 2014. Antiinflammatory activity of glucomoringin isothiocyanate in a mouse model of experimental autoimmune encephalomyelitis. Fitoterapia 95, 160–174.
Gao, Z., Wen, Q., Xia, Y., Yang, J., Gao, P., Zhang, N., et al., 2014. Osthole augments therapeutic efficiency of neural stem cells-based therapy in experimental autoimmune encephalomyelitis. J. Pharmacol. Sci. 124 (1), 54–65.
Ge, Y., Jensen, J.H., Lu, H., Helpern, J.A., Miles, L., Inglese, M., et al., 2007. Quantitative assessment of iron accumulation in the deep gray matter of multiple sclerosis by magnetic field correlation imaging. AJNR Am. J. Neuroradiol. 28 (9), 1639–1644.
Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J.Z., Xie, X.Q., et al., 2008. Beta-caryophyllene is a dietary cannabinoid. Proc. Natl. Acad. Sci. U. S. A. 105 (26), 9099–9104.
Ghaiad, H.R., Nooh, M.M., El-Sawalhi, M.M., Shaheen, A.A., 2017. Resveratrol promotes remyelination in cuprizone model of multiple sclerosis: biochemical and histological study. Mol. Neurobiol. 54 (5), 3219–3229.
Gharagozloo, M., Velardi, E., Bruscoli, S., Agostini, M., Di Sante, M., Donato, V., et al., 2010. Silymarin suppress CD4+ T cell activation and proliferation: effects on NF-κB activity and IL-2 production. Pharmacol. Res. 61 (5), 405–409.
Gharagozloo, M., Javid, E.N., Rezaei, A., Mousavizadeh, K., 2013. Silymarin inhibits cell cycle progression and mTOR activity in activated human T cells: therapeutic implications for autoimmune diseases. Basic Clin. Pharmacol. Toxicol. 112 (4), 251–256.
Ghazavi, A., Mosayebi, G., Salehi, H., Abtahi, H., 2009. Effect of ethanol extract of saffron (*Crocus sativus* L.) on the inhibition of experimental autoimmune encephalomyelitis in C57bl/6 mice. Pak. J. Biol. Sci. 12 (9), 690–695.
Giacoppo, S., Soundara Rajan, T., Galuppo, M., Pollastro, F., Grassi, G., Bramanti, P., et al., 2015a. Purified cannabidiol, the main non-psychotropic component of *Cannabis sativa*, alone, counteracts neuronal apoptosis in experimental multiple sclerosis. Eur. Rev. Med. Pharmacol. Sci. 19 (24), 4906–4919.
Giacoppo, S., Galuppo, M., Pollastro, F., Grassi, G., Bramanti, P., Mazzon, E., 2015b. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. Daru 23, 48.
Giacoppo, S., Soundara Rajan, T., De Nicola, G.R., Iori, R., Bramanti, P., Mazzon, E., 2016. Moringin activates Wnt canonical pathway by inhibiting GSK3β in a mouse model of experimental autoimmune encephalomyelitis. Drug Des. Dev. Ther. 10, 3291–3304.
Gilgun-Sherki, Y., Melamed, E., Offen, D., 2004. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J. Neurol. 251 (3), 261–268.
Gu, B., Zeng, Y., Yin, C., Wang, H., Yang, X., Wang, S., et al., 2012. Sinomenine reduces iNOS expression via inhibiting the T-bet IFN-γ pathway in experimental autoimmune encephalomyelitis in rats. J. Biomed. Res. 26 (6), 448–455.
Haghmorad, D., Mahmoudi, M.B., Salehipour, Z., Jalayer, Z., Momtazi brojeni, A.A., Rastin, M., et al., 2017. Hesperidin ameliorates immunological outcome and reduces neuroinflammation in the mouse model of multiple sclerosis. J. Neuroimmunol. 302, 23–33.
Haider, L., Fischer, M.T., Frischer, J.M., Bauer, J., Hoftberger, R., Botond, G., et al., 2011. Oxidative damage in multiple sclerosis lesions. Brain 134, 1914–1924.
Hametner, S., Wimmer, I., Haider, L., Pfeifenbring, S., Bruck, W., Lassmann, H., 2013. Iron and neurodegeneration in the multiple sclerosis brain. Ann. Neurol. 74 (6),

848–861.
Hanson, J.R., 2003. Natural Products: the Secondary Metabolites. Royal Society of Chemistry, pp. 1–34.
Harbige, L.S., Layward, L., Morris-Downes, M.M., Dumonde, D.C., Amor, S., 2000. The protective effects of omega-6 fatty acids in experimental autoimmune encephalomyelitis (EAE) in relation to transforming growth factor-beta 1 (TGF-β1) up-regulation and increased prostaglandin E_2 (PGE_2) production. Clin. Exp. Immunol. 122 (3), 445–452.
Hardardottir, I., Olafsdottir, E.S., Freysdottir, J., 2015. Dendritic cells matured in the presence of the *Lycopodium* alkaloid annotine direct T cell responses toward a Th2/Treg phenotype. Phytomedicine 22 (2), 277–282.
He, Y., Du, M., Gao, Y., Liu, H., Wang, H., Wu, X., et al., 2013. Astragaloside IV attenuates experimental autoimmune encephalomyelitis of mice by counteracting oxidative stress at multiple levels. PLoS One 8 (10), e76495.
Hegazy, H.G., Ali, E.H.A., Sabry, H.A., 2016. The neuroprotective action of naringenin on oseltamivir (Tamiflu) treated male rats. J. Basic Appl. Zool. 77 (Suppl. C), 83–90.
Hemmer, B., Nessler, S., Zhou, D., Kieseier, B., Hartung, H.P., 2006. Immunopathogenesis and immunotherapy of multiple sclerosis. Nat. Clin. Pract. Neurol. 2 (4), 201–211.
Hikim, A.P.S., Lue, Y.H., Wang, C., Reutrakul, V., Sangsuwan, R., Swerdloff, R.S., 2000. Posttesticular Antifertility action of triptolide in the male eat: evidence for severe impairment of cauda epididymal sperm ultrastructure. J. Androl. 21 (3), 431–437.
Horstmann, B., Zinser, E., Turza, N., Kerek, F., Steinkasserer, A., 2008. MCS-18, a novel natural product isolated from *Helleborus purpurascens*, inhibits dendritic cell activation and prevents autoimmunity as shown *in vivo* using the EAE model. Immunobiology 212 (9), 839–853.
Hou, L.F., He, S.J., Li, X., Yang, Y., He, P.L., Zhou, Y., et al., 2011. Oral administration of artemisinin analog SM934 ameliorates lupus syndromes in MRL/lpr mice by inhibiting Th1 and Th17 cell responses. Arthritis Rheum. 63 (8), 2445–2455.
Hou, L.F., He, S.J., Li, X., Wan, C.P., Yang, Y., Zhang, X.H., et al., 2012. SM934 treated lupus-prone NZB × NZW F1 mice by enhancing macrophage interleukin-10 production and suppressing pathogenic T cell development. PLoS One 7 (2), e32424.
Hu, P., Ma, L., Wang, Y.G., Ye, F., Wang, C., Zhou, W.H., et al., 2017. Genistein, a dietary soy isoflavone, exerts antidepressant-like effects in mice: involvement of serotonergic system. Neurochem. Int. 108, 426–435.
Huynh, P.N., Hikim, A.P., Wang, C., Stefonovic, K., Lue, Y.H., Leung, A., et al., 2000. Long-term effects of triptolide on spermatogenesis, epididymal sperm function, and fertility in male rats. J. Androl. 21 (5), 689–699.
Ilhan, A., Akyol, O., Gurel, A., Armutcu, F., Iraz, M., Oztas, E., 2004. Protective effects of caffeic acid phenethyl ester against experimental allergic encephalomyelitis-induced oxidative stress in rats. Free Radic. Biol. Med. 37 (3), 386–394.
Imler Jr., T.J., Petro, T.M., 2009. Decreased severity of experimental autoimmune encephalomyelitis during resveratrol administration is associated with increased IL-17 + IL-10 + T cells, CD4(-) IFN-γ + cells, and decreased macrophage IL-6 expression. Int. Immunopharmacol. 9 (1), 134–143.
Iruretagoyena, M.I., Tobar, J.A., Gonzalez, P.A., Sepulveda, S.E., Figueroa, C.A., Burgos, R.A., et al., 2005. Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse. J. Pharmacol. Exp. Ther. 312 (1), 366–372.
Iruretagoyena, M.I., Sepulveda, S.E., Lezana, J.P., Hermoso, M., Bronfman, M., Gutierrez, M.A., et al., 2006. Inhibition of nuclear factor-kappa B enhances the capacity of immature dendritic cells to induce antigen-specific tolerance in experimental autoimmune encephalomyelitis. J. Pharmacol. Exp. Ther. 318 (1), 59–67.
Jafarzadeh, A., Mohammadi-Kordkhayli, M., Ahangar-Parvin, R., Azizi, V., Khoramdel-Azad, H., Shamsizadeh, A., et al., 2014. Ginger extracts influence the expression of IL-27 and IL-33 in the central nervous system in experimental autoimmune encephalomyelitis and ameliorates the clinical symptoms of disease. J. Neuroimmunol. 276 (1), 80–88.
Jahromi, S.R., Arrefhosseini, S.R., Ghaemi, A., Alizadeh, A., Sabetghadam, F., Togha, M., 2014. Effect of oral genistein administration in early and late phases of allergic encephalomyelitis. Iran J. Basic Med. Sci. 17 (7), 509–515.
Jia, Y., Jing, J., Bai, Y., Li, Z., Liu, L., Luo, J., et al., 2011. Amelioration of experimental autoimmune encephalomyelitis by plumbagin through down-regulation of JAK-STAT and NF-κB signaling pathways. PLoS One 6 (10), e27006.
Jia, Y., Li, Z., Cai, W., Xiao, D., Han, S., Han, F., et al., 2018. SIRT1 regulates inflammation response of macrophages in sepsis mediated by long noncoding RNA. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1864 (3), 784–792.
Jiang, Y., Wu, A., Zhu, C., Pi, R., Chen, S., Liu, Y., et al., 2013. The protective effect of berberine against neuronal damage by inhibiting matrix metalloproteinase-9 and laminin degradation in experimental autoimmune encephalomyelitis. Neurol. Res. 35 (4), 360–368.
Kan, Q.C., Zhu, L., Liu, N., Zhang, G.X., 2013. Matrine suppresses expression of adhesion molecules and chemokines as a mechanism underlying its therapeutic effect in CNS autoimmunity. Immunol. Res. 56 (1), 189–196.
Kan, Q.C., Zhang, S., Xu, Y.M., Zhang, G.X., Zhu, L., 2014. Matrine regulates glutamate-related excitotoxic factors in experimental autoimmune encephalomyelitis. Neurosci. Lett. 560, 92–97.
Kan, Q.C., Lv, P., Zhang, X.J., Xu, Y.M., Zhang, G.X., Zhu, L., 2015. Matrine protects neuro-axon from CNS inflammation-induced injury. Exp. Mol. Pathol. 98 (1), 124–130.
Kanakasabai, S., Casalini, E., Walline, C.C., Mo, C., Chearwae, W., Bright, J.J., 2012. Differential regulation of CD4(+) T helper cell responses by curcumin in experimental autoimmune encephalomyelitis. J. Nutr. Biochem. 23 (11), 1498–1507.
Kizelsztein, P., Komarnytsky, S., Raskin, I., 2009. Oral administration of triptolide ameliorates the clinical signs of experimental autoimmune encephalomyelitis (EAE) by induction of HSP70 and stabilization of NF-κB/IκBα transcriptional complex. J. Neuroimmunol. 217 (1–2), 28–37.
Klauke, A.L., Racz, I., Pradier, B., Markert, A., Zimmer, A.M., Gertsch, J., et al., 2014. The cannabinoid CB2 receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain. Eur. Neuropsychopharmacol. 24 (4), 608–620.
Klein, T.W., 2005. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat. Rev. Immunol. 5, 400.
Kotzin, B.L., Leung, D.Y.M., Kappler, J., Marrack, P., 1993. Superantigens and their potential role in human disease. In: In: Dixon, F.J. (Ed.), Advances in Immunology, vol. 54. Academic Press, pp. 99–166.
Kouakou, K., Schepetkin, I.A., Jun, S., Kirpotina, L.N., Yapi, A., Khramova, D.S., et al., 2013. Immunomodulatory activity of polysaccharides isolated from *Clerodendrum splendens*: beneficial effects in experimental autoimmune encephalomyelitis. BMC Complement Altern. Med. 13, 149.
Kozela, E., Lev, N., Kaushansky, N., Eilam, R., Rimmerman, N., Levy, R., et al., 2011. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. Br. J. Pharmacol. 163 (7), 1507–1519.
Ku, C.M., Lin, J.Y., 2013. Anti-inflammatory effects of 27 selected terpenoid compounds tested through modulating Th1/Th2 cytokine secretion profiles using murine primary splenocytes. Food Chem. 141 (2), 1104–1113.
Kuo, C.L., Chi, C.W., Liu, T.Y., 2004. The anti-inflammatory potential of berberine *in vitro* and *in vivo*. Cancer Lett. 203 (2), 127–137.
Lassmann, H., 2014. Multiple sclerosis: lessons from molecular neuropathology. Exp. Neurol. 262, 2–7.
Leger, O.J., Yednock, T.A., Tanner, L., Horner, H.C., Hines, D.K., Keen, S., et al., 1997. Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis. Hum. Antib. 8 (1), 3–16.
Leray, E., Moreau, T., Fromont, A., Edan, G., 2016. Epidemiology of multiple sclerosis. Rev. Neurol. (Paris) 172 (1), 3–13.
Leuschner, J.T., Harvey, D.J., Bullingham, R.E., Paton, W.D., 1986. Pharmacokinetics of delta 9-tetrahydrocannabinol in rabbits following single or multiple intravenous doses. Drug Metab. Dispos. 14 (2), 230–238.
Li, T., Wong, V.K., Yi, X.Q., Wong, Y.F., Zhou, H., Liu, L., 2010. Matrine induces cell anergy in human Jurkat T cells through modulation of mitogen-activated protein kinases and nuclear factor of activated T-cells signaling with concomitant up-regulation of anergy-associated genes expression. Biol. Pharm. Bull. 33 (1), 40–46.
Li, X., Li, T.T., Zhang, X.H., Hou, L.F., Yang, X.Q., Zhu, F.H., et al., 2013. Artemisinin analogue SM934 ameliorates murine experimental autoimmune encephalomyelitis through enhancing the expansion and functions of regulatory T cell. PLoS One 8 (8), e74108.
Li, Z., Ji, H., Song, X., Hu, J., Han, N., Chen, N., 2014. Osthole attenuates the development of carrageenan-induced lung inflammation in rats. Int. Immunopharmacol. 20 (1), 33–36.
Li, W., Zhang, Z., Zhang, K., Xue, Z., Li, Y., Zhang, Z., et al., 2016a. Arctigenin suppress Th17 cells and ameliorates experimental autoimmune encephalomyelitis through AMPK and PPAR-γ/ROR-γt signaling. Mol. Neurobiol. 53 (8), 5356–5366.
Li, X., Zhang, Y., Yan, Y., Ciric, B., Ma, C.G., Gran, B., et al., 2016b. Neural stem cells engineered to express three therapeutic factors mediate recovery from chronic stage CNS autoimmunity. Mol. Ther. 24 (8), 1456–1469.
Li, X., Zhao, L., Han, J.-J., Zhang, F., Liu, S., Zhu, L., et al., 2018. Carnosol modulates Th17 cell differentiation and microglial switch in experimental autoimmune encephalomyelitis. Front. Immunol. 9, 1807.
Li-Weber, M., 2009. New therapeutic aspects of flavones: the anticancer properties of *Scutellaria* and its main active constituents wogonin, baicalein and baicalin. Cancer Treat Rev. 35 (1), 57–68.
Liang, M., Chen, Y., Zhang, L., Li, L., Chen, G., Yin, L., 2015. *Epimedium* flavonoids ameliorate neuropathological changes and increases IGF-1 expression in C57BL/6 mice exposed to cuprizone. Neurochem. Res. 40 (3), 492–500.
Ma, X., Jiang, Y., Wu, A., Chen, X., Pi, R., Liu, M., et al., 2010. Berberine attenuates experimental autoimmune encephalomyelitis in C57 BL/6 mice. PLoS One 5 (10), e13489.
Mahad, D.J., Ziabreva, I., Campbell, G., Lax, N., White, K., Hanson, P.S., et al., 2009. Mitochondrial changes within axons in multiple sclerosis. Brain 132 (Pt 5), 1161–1174.
Mahad, D.H., Trapp, B.D., Lassmann, H., 2015. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 14 (2), 183–193.
Mahmoodi, M., Amiri, H., Ayoobi, F., Rahmani, M., Taghipour, Z., Ghavamabadi, R.T., et al., 2019a. Carvacrol ameliorates experimental autoimmune encephalomyelitis through modulating pro- and anti-inflammatory cytokines. Life Sci. 219, 257–263.
Mahmoodi, M., Ayoobi, F., Aghaei, A., Rahmani, M., Taghipour, Z., Hosseini, A., et al., 2019b. Beneficial effects of *Thymus vulgaris* extract in experimental autoimmune encephalomyelitis: clinical, histological and cytokine alterations. Biomed. Pharmacother. 109, 2100–2108.
Martin, R., Carvalho-Tavares, J., Hernandez, M., Arnes, M., Ruiz-Gutierrez, V., Nieto, M.L., 2010. Beneficial actions of oleanolic acid in an experimental model of multiple sclerosis: a potential therapeutic role. Biochem. Pharmacol. 79 (2), 198–208.
Martin, R., Hernandez, M., Cordova, C., Nieto, M.L., 2012. Natural triterpenes modulate immune-inflammatory markers of experimental autoimmune encephalomyelitis: therapeutic implications for multiple sclerosis. Br. J. Pharmacol. 166 (5), 1708–1723.
McPartland, J., Russo, E., 2001. *Cannabis* and *Cannabis* extracts: greater than the sum of their parts? J. Cannabis Ther. 1, 103–132.
Miljkovic, D., Dekanski, D., Miljkovic, Z., Momcilovic, M., Mostarica-Stojkovic, M., 2009. Dry olive leaf extract ameliorates experimental autoimmune encephalomyelitis. Clin. Nutr. 28 (3), 346–350.
Min, K., Yoon, W.K., Kim, S.K., Kim, B.H., 2007. Immunosuppressive effect of silibinin in experimental autoimmune encephalomyelitis. Arch Pharm. Res. (Seoul) 30 (10),

1265–1272.
Miyake, Y., Kozutsumi, Y., Nakamura, S., Fujita, T., Kawasaki, T., 1995. Serine palmitoyltransferase is the primary target of a sphingosine-like immunosuppressant, ISP-1/Myriocin. Biochem. Biophys. Res. Commun. 211 (2), 396–403.
Miyake, M., Sasaki, K., Ide, K., Matsukura, Y., Shijima, K., Fujiwara, D., 2006. Highly oligomeric procyanidins ameliorate experimental autoimmune encephalomyelitis via suppression of Th1 immunity. J. Immunol. 176 (10), 5797–5804.
Mohamed, A., Shoker, A., Bendjelloul, F., Mare, A., Alzrigh, M., Benghuzzi, H., et al., 2003. Improvement of experimental allergic encephalomyelitis (EAE) by thymoquinone; an oxidative stress inhibitor. Interleukins (IL-7 and IL-7r) gene expression and thymoquinones role in the amelioration of eae symptoms. 39, 440–445.
Mosayebi, G., Ghazavi, A., Salehi, H., Payani, M.A., Khazae, M.R., 2007. Effect of sesame oil on the inhibition of experimental autoimmune encephalomyelitis in C57BL/6 mice. Pak. J. Biol. Sci. 10 (11), 1790–1796.
Noor, N.A., Fahmy, H.M., Mohammed, F.F., Elsayed, A.A., Radwan, N.M., 2015. *Nigella sativa* amliorates inflammation and demyelination in the experimental autoimmune encephalomyelitis-induced Wistar rats. Int. J. Clin. Exp. Pathol. 8 (6), 6269–6286.
Ousman, S.S., Tomooka, B.H., van Noort, J.M., Wawrousek, E.F., O'Connor, K.C., Hafler, D.A., et al., 2007. Protective and therapeutic role for αB-crystallin in autoimmune demyelination. Nature 448 (7152), 474–479.
Ozgun-Acar, O., Celik-Turgut, G., Gazioglu, I., Kolak, U., Ozbal, S., Ergur, B.U., et al., 2016. *Capparis ovata* treatment suppresses inflammatory cytokine expression and ameliorates experimental allergic encephalomyelitis model of multiple sclerosis in C57BL/6 mice. J. Neuroimmunol. 298, 106–116.
Pareek, T.K., Belkadi, A., Kesavapany, S., Zaremba, A., Loh, S.L., Bai, L., et al., 2011. Triterpenoid modulation of IL-17 and Nrf-2 expression ameliorates neuroinflammation and promotes remyelination in autoimmune encephalomyelitis. Sci. Rep. 1, 201.
Petro, T.M., 2011. Regulatory role of resveratrol on Th17 in autoimmune disease. Int. Immunopharmacol. 11 (3), 310–318.
Pockley, A.G., 2003. Heat shock proteins as regulators of the immune response. Lancet 362 (9382), 469–476.
Powell, M.B., Mitchell, D., Lederman, J., Buckmeier, J., Zamvil, S.S., Graham, M., et al., 1990. Lymphotoxin and tumor necrosis factor-alpha production by myelin basic protein-specific T cell clones correlates with encephalitogenicity. Int. Immunol. 2 (6), 539–544.
Qin, X., Guo, B.T., Wan, B., Fang, L., Lu, L., Wu, L., et al., 2010. Regulation of Th1 and Th17 cell differentiation and amelioration of experimental autoimmune encephalomyelitis by natural product compound berberine. J. Immunol. 185 (3), 1855–1863.
Qu, Z., Zheng, N., Zhang, Y., Zhang, L., Liu, J., Wang, Q., et al., 2016. Preventing the BDNF and NGF loss involved in the effects of cornel iridoid glycoside on attenuation of experimental autoimmune encephalomyelitis in mice. Neurol. Res. 38 (9), 831–837.
Raffa, D., Maggio, B., Raimondi, M.V., Plescia, F., Daidone, G., 2017. Recent discoveries of anticancer flavonoids. Eur. J. Med. Chem. 142, 213–228.
Rajagopal, S., Kumar, R.A., Deevi, D.S., Satyanarayana, C., Rajagopalan, R., 2003. Andrographolide, a potential cancer therapeutic agent isolated from *Andrographis paniculata*. J. Exp. Ther. Oncol. 3 (3), 147–158.
Rao, P., Segal, B.M., 2012. Experimental autoimmune encephalomyelitis. Methods Mol. Biol. 900, 363–380.
Razeghi, S., Aref Hosseini, S.R., Ebrahimi Mamaghani, M., Togha, M., Roushangar, L., T, A., et al., 2009. Prevention of animal model of multiple sclerosis by oral genistein, extracted from soy bean. Iran J. Neurol. 8, 505–517.
Razeghi Jahromi, S., Arrefhosseini, S.R., Ghaemi, A., Alizadeh, A., Sabetghadam, F., Togha, M., 2014. Effect of oral genistein administration in early and late phases of allergic encephalomyelitis. Iran J. Basic Med. Sci. 17 (7), 509–515.
Ren, Y., Lu, L., Guo, T.B., Qiu, J., Yang, Y., Liu, A., et al., 2008. Novel immunomodulatory properties of berbamine through selective down-regulation of STAT4 and action of IFN-γ in experimental autoimmune encephalomyelitis. J. Immunol. 181 (2), 1491–1498.
Riviere, C., Pawlus, A.D., Merillon, J.M., 2012. Natural stilbenoids: distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. Nat. Prod. Rep. 29 (11), 1317–1333.
Robson, P., 2011. Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opin. Drug Saf. 10 (5), 675–685.
Samoilova, E.B., Horton, J.L., Hilliard, B., Liu, T.S., Chen, Y., 1998. IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: roles of IL-6 in the activation and differentiation of autoreactive T cells. J. Immunol. 161 (12), 6480–6486.
Sato, F., Martinez, N.E., Shahid, M., Rose, J.W., Carlson, N.G., Tsunoda, I., 2013. Resveratrol exacerbates both autoimmune and viral models of multiple sclerosis. Am. J. Pathol. 183 (5), 1390–1396.
Scott, A., Higdon, K., Tucci, M., Benghuzzi, H., Puckett, A., Tsao, A., et al., 2001. The prevention of osteoporotic progression by means of steroid loaded TCPL drug delivery systems. Biomed. Sci. Instrum. 37, 13–18.
Shakeri, A., Sahebkar, A., Javadi, B., 2016. *Melissa officinalis* L.-A review of its traditional uses, phytochemistry and pharmacology. J. Ethnopharmacol. 188, 204–228.
Shen, R., Deng, W., Li, C., Zeng, G., 2015. A natural flavonoid glucoside icariin inhibits Th1 and Th17 cell differentiation and ameliorates experimental autoimmune encephalomyelitis. Int. Immunopharmacol. 24 (2), 224–231.
Shindler, K.S., Ventura, E., Dutt, M., Elliott, P., Fitzgerald, D.C., Rostami, A., 2010. Oral resveratrol reduces neuronal damage in a model of multiple sclerosis. J. Neuro Ophthalmol. 30 (4), 328–339.
Showalter, V.M., Compton, D.R., Martin, B.R., Abood, M.E., 1996. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. J. Pharmacol. Exp. Ther. 278 (3), 989–999.
Soderstrom, M., 2001. Optic neuritis and multiple sclerosis. Acta Ophthalmol. Scand. 79 (3), 223–227.
Spate, S., Ramadan, H.H., Mohamed, A., 2010. Interleukins (IL-7 and IL-7r) gene expression and thymoquinones role in the amelioration of eae symptoms - biomed 2010. Biomed. Sci. Instrum. 46 190-85.
Stadelmann, C., Wegner, C., Bruck, W., 2011. Inflammation, demyelination, and degeneration - recent insights from MS pathology. Biochim. Biophys. Acta 1812 (2), 275–282.
Stürner, K.H., Verse, N., Yousef, S., Martin, R., Sospedra, M., 2014. Boswellic acids reduce Th17 differentiation via blockade of IL-1β-mediated IRAK1 signaling. Eur. J. Immunol. 44 (4), 1200–1212.
Sun, Y.Z., Chen, J.F., Shen, L.M., Zhou, J., Wang, C.F., 2017. Anti-atherosclerotic effect of hesperidin in LDLr−/− mice and its possible mechanism. Eur. J. Pharmacol. 815 (Suppl. C), 109–117.
Tan, P., Zhong, W., Cai, W., 2000. Clinical study on treatment of 40 cases of malignant brain tumor by elemene emulsion injection. Zhongguo Zhong Xi Yi Jie He Za Zhi 20 (9), 645–648.
Tian, G.X., Zhu, X.Q., Chen, Y., Wu, G.C., Wang, J., 2013. Huperzine A inhibits CCL2 production in experimental autoimmune encephalomyelitis mice and in cultured astrocyte. Int. J. Immunopathol. Pharmacol. 26 (3), 757–764.
Tran, T.A., McCoy, M.K., Sporn, M.B., Tansey, M.G., 2008. The synthetic triterpenoid CDDO-methyl ester modulates microglial activities, inhibits TNF production, and provides dopaminergic neuroprotection. J. Neuroinflammation 5, 14.
Tullman, M.J., 2013. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am. J. Manag. Care 19 (2 Suppl. l), S15–S20.
Ungerleider, J.T., Andyrsiak, T., Fairbanks, L., Ellison, G.W., Myers, L.W., 1987. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv. Alcohol Subst. Abuse 7 (1), 39–50.
Vazirinejad, R., Ayoobi, F., Arababadi, M.K., Eftekharian, M.M., Darekordi, A., Goudarzvand, M., et al., 2014. Effect of aqueous extract of *Achillea millefolium* on the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. Indian J. Pharmacol. 46 (3), 303–308.
Veiga, V.F., Rosas, E.C., Carvalho, M.V., Henriques, M.G.M.O., Pinto, A.C., 2007. Chemical composition and anti-inflammatory activity of copaiba oils from *Copaifera cearensis* Huber ex Ducke, *Copaifera reticulata* Ducke and *Copaifera multijuga* Hayne—a comparative study. J. Ethnopharmacol. 112 (2), 248–254.
Verbeek, R., van Tol, E.A., van Noort, J.M., 2005. Oral flavonoids delay recovery from experimental autoimmune encephalomyelitis in SJL mice. Biochem. Pharmacol. 70 (2), 220–228.
Wade, D.T., Robson, P., House, H., Makela, P., Aram, J., 2003. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin. Rehabil. 17 (1), 21–29.
Wade, D.T., Makela, P., Robson, P., House, H., Bateman, C., 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult. Scler. 10 (4), 434–441.
Wang, J., Zhang, H., Sun, Y., 1996. Phase III clinical trial of elemenum emulsion in the management of malignant pleural and peritoneal effusions. Zhonghua Zhongliu Zazhi 18 (6), 464–467.
Wang, Z., Qiu, J., Guo, T.B., Liu, A., Wang, Y., Li, Y., et al., 2007. Anti-inflammatory properties and regulatory mechanism of a novel derivative of artemisinin in experimental autoimmune encephalomyelitis. J. Immunol. 179 (9), 5958–5965.
Wang, Y., Mei, Y., Feng, D., Xu, L., 2008. Triptolide modulates T-cell inflammatory responses and ameliorates experimental autoimmune encephalomyelitis. J. Neurosci. Res. 86 (11), 2441–2449.
Wang, J., Chen, F., Zheng, P., Deng, W., Yuan, J., Peng, B., et al., 2012. Huperzine A ameliorates experimental autoimmune encephalomyelitis via the suppression of T cell-mediated neuronal inflammation in mice. Exp. Neurol. 236 (1), 79–87.
Wang, Y., Cao, L., Xu, L.M., Cao, F.F., Peng, B., Zhang, X., et al., 2015. Celastrol ameliorates EAE induction by suppressing pathogenic T cell responses in the peripheral and central nervous systems. J. Neuroimmune Pharmacol. 10 (3), 506–516.
Wang, D., Li, S.P., Fu, J.S., Bai, L., Guo, L., 2016. Resveratrol augments therapeutic efficiency of mouse bone marrow mesenchymal stem cell-based therapy in experimental autoimmune encephalomyelitis. Int. J. Dev. Neurosci. 49, 60–66.
Wang, J., Qi, Y., Niu, X., Tang, H., Meydani, S.N., Wu, D., 2018a. Dietary naringenin supplementation attenuates experimental autoimmune encephalomyelitis by modulating autoimmune inflammatory responses in mice. J. Nutr. Biochem. 54, 130–139.
Wang, B., Zheng, X., Liu, J., Zhang, Z., Qiu, C., Yang, L., et al., 2018b. Osthole inhibits pancreatic cancer progression by directly exerting negative effects on cancer cells and attenuating tumor-infiltrating M2 macrophages. J. Pharmacol. Sci. 137 (3), 290–298.
Wei, Z., Deng, X., Hong, M., Su, Q., Liu, A., Huang, Y., et al., 2015. Icariin has synergistic effects with methylprednisolone to ameliorate EAE via modulating HPA function, promoting anti-inflammatory and anti-apoptotic effects. Int. J. Clin. Exp. Med. 8 (11), 20188–20197.
Wight, R.D., Tull, C.A., Deel, M.W., Stroope, B.L., Eubanks, A.G., Chavis, J.A., et al., 2012. Resveratrol effects on astrocyte function: relevance to neurodegenerative diseases. Biochem. Biophys. Res. Commun. 426 (1), 112–115.
Wildfeuer, A., Neu, I.S., Safayhi, H., Metzger, G., Wehrmann, M., Vogel, U., et al., 1998. Effects of boswellic acids extracted from a herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis. Arzneimittelforschung 48 (6), 668–674.
Wu, W., Liu, K., Tang, X., 1999. Preliminary study on the antitumor immuno-protective mechanism of beta-elemene. Zhonghua Zhongliu Zazhi 21 (6), 405–408.
Xia, Y.F., Ye, B.Q., Li, Y.D., Wang, J.G., He, X.J., Lin, X., et al., 2004. Andrographolide attenuates inflammation by inhibition of NF-κ B activation through covalent

modification of reduced cysteine 62 of p50. J. Immunol. 173 (6), 4207–4217.
Xiao, L., Guo, D., Hu, C., Shen, W., Shan, L., Li, C., et al., 2012. Diosgenin promotes oligodendrocyte progenitor cell differentiation through estrogen receptor-mediated ERK1/2 activation to accelerate remyelination. Glia 60 (7), 1037–1052.
Xiao, J., Yang, R., Yang, L., Fan, X., Liu, W., Deng, W., 2015. Kirenol attenuates experimental autoimmune encephalomyelitis by inhibiting differentiation of Th1 and th17 cells and inducing apoptosis of effector T cells. Sci. Rep. 5, 9022.
Xie, L., Li, X.K., Funeshima-Fuji, N., Kimura, H., Matsumoto, Y., Isaka, Y., et al., 2009. Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. Int. Immunopharmacol. 9 (5), 575–581.
Xin, J., Feinstein, D.L., Hejna, M.J., Lorens, S.A., McGuire, S.O., 2012. Beneficial effects of blueberries in experimental autoimmune encephalomyelitis. J. Agric. Food Chem. 60 (23), 5743–5748.
Xu, J., Huang, R., Yang, Y.J., Jin, S.J., Zhang, J.F., 2011. Effects of baicalin on apoptosis in rats with autoimmune encephalomyelitis. Zhong Guo Dang Dai Er Ke Za Zhi 13 (8), 665–668.
Xue, Z., Ge, Z., Zhang, K., Sun, R., Yang, J., Han, R., et al., 2014. Embelin suppresses dendritic cell functions and limits autoimmune encephalomyelitis through the TGF-β/β-catenin and STAT3 signaling pathways. Mol. Neurobiol. 49 (2), 1087–1101.
Yan, L.C., Bi, E.G., Lou, Y.T., Wu, X.D., Liu, Z.D., Zou, J., et al., 2010. Novel sinomenine derivative 1032 improves immune suppression in experimental autoimmune encephalomyelitis. Biochem. Biophys. Res. Commun. 391 (1), 1093–1098.
Yang, H., Liu, C., Jiang, J., Wang, Y., Zhang, X., 2017. Celastrol attenuates multiple sclerosis and optic neuritis in an experimental autoimmune encephalomyelitis model. Front. Pharmacol. 8, 44.
Yao, W., Wang, F., Wang, H., 2016. Immunomodulation of artemisinin and its derivatives. Sci. Bull. 61 (18), 1399–1406.
Yin, L.L., Lin, L.L., Zhang, L., Li, L., 2012. *Epimedium* flavonoids ameliorate experimental autoimmune encephalomyelitis in rats by modulating neuroinflammatory and neurotrophic responses. Neuropharmacology 63 (5), 851–862.
Yin, L., Chen, Y., Qu, Z., Zhang, L., Wang, Q., Zhang, Q., et al., 2014. Involvement of JAK/STAT signaling in the effect of cornel iridoid glycoside on experimental autoimmune encephalomyelitis amelioration in rats. J. Neuroimmunol. 274 (1–2), 28–37.
Yue, Y., Stone, S., Lin, W., 2018. Role of nuclear factor κB in multiple sclerosis and experimental autoimmune encephalomyelitis. Neurol. Regen. Res. 13 (9), 1507–1515.
Zeng, Y., Song, C., Ding, X., Ji, X., Yi, L., Zhu, K., 2007a. Baicalin reduces the severity of experimental autoimmune encephalomyelitis. Braz. J. Med. Biol. Res. 40 (7), 1003–1010.
Zeng, Y., Gu, B., Ji, X., Ding, X., Song, C., Wu, F., 2007b. Sinomenine, an antirheumatic alkaloid, ameliorates clinical signs of disease in the Lewis rat model of acute experimental autoimmune encephalolmyelitis. Biol. Pharm. Bull. 30 (8), 1438–1444.
Zhang, Y., Wang, S., Li, Y., Xiao, Z., Hu, Z., Zhang, J., 2008. Sophocarpine and matrine inhibit the production of TNF-α and IL-6 in murine macrophages and prevent cachexia-related symptoms induced by colon 26 adenocarcinoma in mice. Int. Immunopharmacol. 8 (13–14), 1767–1772.
Zhang, J., Ni, J., Chen, Z.H., Li, X., Zhang, R.J., Tang, W., et al., 2009. Periplocoside A prevents experimental autoimmune encephalomyelitis by suppressing IL-17 production and inhibits differentiation of Th17 cells. Acta Pharmacol. Sin. 30 (8), 1144–1152.
Zhang, R., Tian, A., Shi, X., Yu, H., Chen, L., 2010. Downregulation of IL-17 and IFN-γ in the optic nerve by β-elemene in experimental autoimmune encephalomyelitis. Int. Immunopharmacol. 10 (7), 738–743.
Zhang, R., Tian, A., Zhang, H., Zhou, Z., Yu, H., Chen, L., 2011. Amelioration of experimental autoimmune encephalomyelitis by β-elemene treatment is associated with Th17 and Treg cell balance. J. Mol. Neurosci. 44 (1), 31–40.
Zhang, S., Kan, Q.C., Xu, Y., Zhang, G.X., Zhu, L., 2013. Inhibitory effect of matrine on blood-brain barrier disruption for the treatment of experimental autoimmune encephalomyelitis. Mediat. Inflamm. 2013, 736085.
Zhang, L., Shen, C., Chu, J., Zhang, R., Li, Y., Li, L., 2014a. Icariin decreases the expression of APP and BACE-1 and reduces the β-amyloid burden in an APP transgenic mouse model of Alzheimer's disease. Int. J. Biol. Sci. 10 (2), 181–191.
Zhang, K., Ge, Z., Da, Y., Wang, D., Liu, Y., Xue, Z., et al., 2014b. Plumbagin suppresses dendritic cell functions and alleviates experimental autoimmune encephalomyelitis. J. Neuroimmunol. 273 (1), 42–52.
Zhang, Y., Li, X., Ciric, B., Ma, C.G., Gran, B., Rostami, A., et al., 2015. Therapeutic effect of baicalin on experimental autoimmune encephalomyelitis is mediated by SOCS3 regulatory pathway. Sci. Rep. 5, 17407.
Zhang, Y., Yin, L., Zheng, N., Zhang, L., Liu, J., Liang, W., et al., 2017. Icariin enhances remyelination process after acute demyelination induced by cuprizone exposure. Brain Res. Bull. 130, 180–187.
Zhao, X., Kan, Q., Zhu, L., Zhang, G.X., 2011. Matrine suppresses production of IL-23/IL-17 and ameliorates experimental autoimmune encephalomyelitis. Am. J. Chin. Med. 39 (5), 933–941.
Zhou, R., Zhang, F., He, P.L., Zhou, W.L., Wu, Q.L., Xu, J.Y., et al., 2005. (5R)-5-hydroxytriptolide (LLDT-8), a novel triptolide analog mediates immunosuppressive effects *in vitro* and *in vivo*. Int. Immunopharmacol. 5 (13–14), 1895–1903.
Zhou, R., Zheng, S.X., Tang, W., He, P.L., Li, X.Y., Yang, Y.F., et al., 2006. Inhibition of inducible nitric-oxide synthase expression by (5R)-5-hydroxytriptolide in interferon-γ- and bacterial lipopolysaccharide-stimulated macrophages. J. Pharmacol. Exp. Ther. 316 (1), 121–128.
Zhu, Y.N., Zhong, X.G., Feng, J.Q., Yang, Y.F., Fu, Y.F., Ni, J., et al., 2006. Periplocoside E inhibits experimental allergic encephalomyelitis by suppressing interleukin 12-dependent CCR5 expression and interferon-γ-dependent CXCR3 expression in T lymphocytes. J. Pharmacol. Exp. Ther. 318 (3), 1153–1162.
Zhu, L., Pan, Q.X., Zhang, X.J., Xu, Y.M., Chu, Y.J., Liu, N., et al., 2016. Protective effects of matrine on experimental autoimmune encephalomyelitis via regulation of ProNGF and NGF signaling. Exp. Mol. Pathol. 100 (2), 337–343.

Glossary

MS: multiple sclerosis
CNS: central nervous system
BBB: blood-brain barrier
Th: T helper cells
SAR: structure-activity relationship
ROS: reactive oxygen species
NO: nitric oxide
ATP: adenosine triphosphate
MRI: magnetic resonance imaging
OPC: oligodendrocyte progenitor cell
VLA-4: very late antigen-4
VCAM-1: vascular cell adhesion molecule-1
IFN-γ: interferon gamma
IL: interleukin
CCL: chemokine (C–C motif) ligand
CXCL: C-X-C motif chemokine
NF-κB: nuclear factor kappa B
TNF-α: tumor necrosis factor alpha
CD: cluster of differentiation
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
PI3K: phosphoinositide 3-kinase
Akt: protein kinase B
mTOR: mechanistic target of rapamycin
p70S6K: ribosomal protein S6 kinase beta-1
p-S6 protein: phospho-S6 ribosomal protein
ROR-γt: RAR-related orphan receptor gamma most studied isoform
Treg: regulatory T cells
PPAR-γ: peroxisome proliferator activated receptor γ
Foxp3: forkhead box p3
AMPK: 5′ AMP-activated protein kinase
GM-CSF: granulocyte-macrophage colony-stimulating factor
SIRT1: Sirtuin 1
CB: cannabinoid receptor
FAS: apoptosis antigen 1 receptor
GFAP: glial fibrillary acidic protein
TGF-β: transforming growth factor beta
JAK/STAT: Janus kinases (JAKs)/signal transducer and activator of transcription proteins (STATs)
iNOS: inducible isoform of nitric oxide synthases
IkBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha that functions to inhibit the NF-κB transcription factor
DC: dendritic cell
GSK3β: glycogen synthase kinase 3 beta
CK2α: protein kinase CK2 alpha
COX2: cyclooxygenase 2
BM-NSC: bone marrow derived neural stem cells
mRNA: messenger RNA
MCP-1: monocyte chemoattractant protein 1
RANTES: chemokine (C–C motif) ligand 5 (also CCL5)
TWEAK: TNF-related weak inducer of apoptosis
ICAM-1: intercellular adhesion molecule 1
TLR4: toll-like receptor 4
MD-2: lymphocyte antigen 96
MMP-9: matrix metallopeptidase 9
CSF: cerebrospinal fluid
MIP-1α: macrophage inflammatory protein alpha
BDNF: brain-derived neurotrophic factor
NGF: nerve growth factor
GSH: glutathione
MOG: myelin oligodendrocyte glycoprotein
MHC: major histocompatibility complex
Nrf2: nuclear factor-like 2
LT: leukotriene
PMNL: polymorphonuclear neutrophil leukocyte
i.p.: intraperitoneal
s.c.: subcutaneous
PBS: phosphate-buffered saline
CMC: carboxy methyl cellulose
p.i.: post-immunization
DMSO: dimethyl sulfoxide
i.g.: intragastric