Journal of the Medical Research Institute

JMRI, 2024; Vol. 45 No. 4: (28-42)

Journal of the Medical Research Institute

The possible therapeutic effects of chlorogenic acid on experimental animal model of multiple sclerosis.

Yousra Yousry Moussa[1*], Al-Sayeda Al-sayed Newairy[1], Fatma El-Rashidy [1],Mennatallah Gowayed[2], Maher A Kamel[3]

1) Biochemistry department, faculty of science, Alexandria University, Alexandria, Egypt.
2) Department of Pharmacology & Toxicology, Faculty of Pharmacy and Drug Manufacturing, Pharos University in Alexandria, Egypt.
3) Biochemistry department, Medical Research Institute, Alexandria University, Alexandria, Egypt.

ABSTRACT:
Multiple Sclerosis (MS) is an inflammatory neurodegenerative disease with distinctive features of focal demyelination, axonal loss, activation of glial cells, and immune cells infiltration. The symptoms of this disease are the consequence of the formation of new lesions in the central nervous system (CNS) and the expansion and aggravation of existing lesions causes its progression. The efficiency of current therapeutic approaches for MS is usually limited by the side effects. Chlorogenic acid (CA) is a natural compound found in a wide range of plant materials and is used in the prevention of many diseases. This review presents preclinical evidence that supports the use of CA in MS treatment protocols.

Keywords: multiple sclerosis, chlorogenic acid, oxidative stress

INTRODUCTION

Neurodegenerative diseases (NDs) encompass several sporadic and/or familial disorders that affect the central nervous system (CNS). These disorders are identified by the occurrence of a vicious cycle of neuronal and synaptic dysfunction in the CNS, with the outcome being irreversible neuronal degeneration (Choonara et al., 2009). The main complications induced by this neuronal degeneration are permanent or temporary impairment in memory, cognitive, sensory, behavioral and/or motor functions (Wilson et al., 2023). Currently, these NDs are incurable. The existing treatments for NDs aim to prevent the aggravation of their complications, prevent permanent disabilities, and enhance the quality of patients' lives (Shusharina et al., 2023).

Multiple Sclerosis

Multiple Sclerosis (MS) is the most prevalent progressive ND among young adults in the world (Evans et al., 2013; Feigin et al., 2017). It is a chronic disease of the CNS where neurodegeneration occurs in correspondence with inflammatory and demyelinating features (Gandhi et al., 2010). MS affects approximately 2.8 million individuals around the world with a continuously rising prevalence (Walton et al., 2020). Several factors have been identified to affect MS incidence, such as genetic composition, biological sex, and geographic location (Simpson et al., 2019). North America and Europe have the largest prevalence of MS incidence (Simpson et al., 2019; Walton et al., 2020). The identification of other early predictors of MS may drastically improve the long-term outcome of MS (Confavreux et al., 2000).

Pathogenesis of Multiple Sclerosis

The pathogenesis of MS includes the disruption of the blood brain barrier (BBB), multifocal inflammation, demyelination, and reactive gliosis in addition to the loss of oligodendrocyte and axonal function (Trapp and Nave, 2008). The pathogenesis of MS is mediated by various molecular mechanisms and the most prominent of these mechanisms is the autoimmune response (Figure 1) (Baecher-Allan et al., 2018; Paudel et al., 2019). The golden target of MS therapies is to suppress the pathological autoimmune responses while the adaptive immune responses remain uncompromised (Paudel et al., 2019).

MS is characterized by inflammatory and demyelination features where an orchestra of many molecular mechanisms work together to induce the disease and later mediate its progression. These molecular mechanisms include the induction of inflammatory responses, activation of glial cells focal demyelination, immune cell infiltration and axonal loss, leading to the formation of lesions which is the hallmark of MS incidence. These newly formed lesions are responsible for the symptoms of MS and the expansion and aggravation of the existing lesions leads to the disease progression (Henderson et al., 2009; Wootla et al., 2012; Popescu et al., 2013).

The possible therapeutic effects of chlorogenic acid on experimental animal model of multiple sclerosis.
Received: 18-12-2024 Accepted: 22-12-2024
Corresponding author: **Yousra Yousry Moussa**

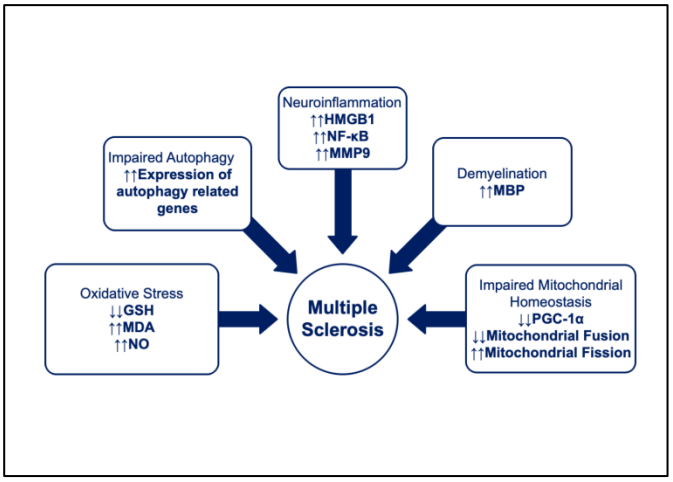


Figure (1):A diagrammatic presentation of the pathogenic mechanisms of multiple sclerosis.
HMGB1: High Mobility Group Box Protein 1, NF-κB: Nuclear Factor kappa B, MMP9: Matrix Metalloproteinase 9, MBP: Myelin Basic Protein, PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha, GSH: Glutathione, MDA: Malondialdehyde, and NO: Nitric Oxide.

MS is conveyed via several autoreactive immune cells that instigate the progressive destruction of myelin and axon which subsequently leads to chronic impairment in sensory and motor functions (Trapp et al., 2008; Lucchinetti et al., 2009). During the pathogenesis of MS, and as the myelin destruction sets in, the axons are exposed and prone to destruction. On the other hand, during remyelination, the compromised axons recover their myelin sheath and regain their function (Franklin, 2002). This remyelination process essentially requires the generation of new oligodendrocytes (OLs). The oligodendrocytes (OLs) are the CNS myelinating cells, and they originate from the oligodendrocyte precursor cells (OPCs) (Keirstead et al., 1997; Watanabe et al., 2002). Moreover, existing mature OLs can contribute to the remyelination process of MS lesions (Duncan et al., 2018). Notably, the remyelination efficiency diminishes as the patient ages and as the severity of the lesions intensifies (Franklin, 2002; Chang et al., 2002; Frischer et al., 2015; Gruchot et al., 2019). The maturation process of OPCs into OLs is critical to supply the neuronal axons with the required structural and metabolic functions (Funfschilling et al., 2012; Lee et al., 2012; Duncan et al., 2021).

Multiple Sclerosis and Neuroinflammation
High Mobility Group Box Protein 1
High mobility group box protein 1 (HMGB1) is a ubiquitous nuclear protein released by glial cells (astrocytes, oligodendrocytes, and microglia) and neurons upon the activation of the inflammasome activation as it is a vital instigator of neuroinflammation (Paudel et al., 2018; Paudel et al., 2019). The HMGB1 has become a hot topic in neuroscience as it represents a viable biomarker of neurological dysfunctions. Furthermore, it is implicated in the pathogenesis of many NDs and traumatic brain injury (Wittkowski et al., 2008; Paudel et al., 2018; Andersson et al., 2018; Paudel et al., 2019). High levels of HMGB1 are reported in MS patients and in experimental autoimmune encephalomyelitis (EAE) models, which illustrates the implication of HMGB1 in the progression of MS (Sun et al., 2015). This crosstalk between HMGB1 and the pathogenesis of MS rendered HMGB1 a golden target for novel therapeutic approaches in managing and treating symptoms of MS.
Nuclear factor kappa B (NF-κB) is another vital mediator of proinflammation. It is strongly implicated in the incidence and progression of MS (Eggert et al., 2008; Yan et al., 2018). NF-κB is a crucial transcription factor that mediates several immune and inflammation cascades (Li et al., 2002; Vallabhapurapu et al., 2009). The activation of NF-κB is regulated by the IKK (IkappaB kinase) complex (Zhang et al., 2017). IKK complex phosphorylates the inhibitor of NF-κB to activate NF-κB and its subsequent signaling pathways (Hayden et al., 2008). The main signaling pathways of NF-κB are identified as canonical (classical) and non-canonical (alternative) pathways (Hayden et al., 2008; Zhou et al., 2020). The canonical or classical signaling pathway of NF-κB is triggered by several proinflammatory cytokines, antigens, and toll-like receptor-binding molecules (Li et al., 2002).
In the case of MS, NF-κB mediates distinct cascades implicated in the pathogenesis of the disease (Ponath et al., 2018). Studies recorded elevation in the level of NF-kB in several blood and immune cell populations obtained from patients suffering from MS (Eggert et al., 2008; Yan et al., 2018). Further studies reported a connection between elevated genes related to NF-kB in T cells and the severity of MS relapsing episodes (Satoh et al., 2008; Lindsey et al., 2011). Moreover, the activation of NF-κB is upregulated in MS lesions, which leads to the disruption of the BBB and the exacerbation of the inflammation status through the excessive production of proinflammatory cytokines. These processes orchestrate MS immune and inflammatory responses leading to even further complications and the progression of the disease (Mc Guire et al., 2013).
Multiple Sclerosis and Demyelination
MS is an inflammatory demyelinating disease of the CNS. Myelin basic protein (MBP) is a membrane-associated protein found in the neuronal axon terminals and is a key element in maintaining the integrity of BBB and insulating axons in the CNS (Aleksandr et al., 2022). MBP is a structural protein that binds to the opposing leaflets of the cytoplasmic side of the oligodendrocyte membrane and ensures that the myelin sheath retains its consistent, compact form (Min et al., 2009; Ahmed et al., 2010).
The MBP exists as eight different charged isoforms. They are known as C1 to C8 forms, and they are products of various post-translational modifications that affect the net charge of MBP, with C1 being the unmodified MBP isoform, which is present in healthy adult myelin. The charges of the other isoforms are altered by various processes such as phosphorylation and deamination or, in the case of C8, by citrullination, which is the conversion of arginine to citrulline (Widder et al., 2020). So, MS is correlated with increased deamination of MBP in the CNS. Therefore, these post-

translational modifications and their consequent modified isoforms are implicated in the pathogenesis of MS, with C8 being the most abundant MBP isoform in MS incidence (Widder et al., 2020; Martinsen et al., 2022).

Another demyelination marker is kallikrein 6 (KLK6), also referred to as Zyme or Neurosin, which is produced essentially by mature OLs in the CNS (Little et al., 1997). The OLs undergo a series of differentiation processes that finally generate the myelinating OLs that wrap axons with a myelin sheath. The role of this myelin sheath is to preserve the structural integrity of neurons and facilitate neuronal signaling (Ferrer, 2018; Stassart et al., 2018). The myelination of CNS occurs late during neural development and takes a long timeframe. The CNS myelination occurs mostly through the first two decades of human life, the last to undergo myelination is the late-maturing brain constituents such as the prefrontal cortex (Mitew et al., 2014).

The KLK6 is implicated in the demyelination process occurring in MS (Scarisbrick et al., 2012; Stassart et al., 2018). Studies documented that increased levels of KLK6 occurred within CNS infiltrating cells such as macrophages and T cells, which were characteristically present at the sites of demyelination in EAE animal models (Scarisbrick et al., 2002; Yoon et al., 2016). In addition, KLK6 levels were elevated in EAE and animal models of stroke and injury of the spinal cord (Terayama et al., 2004; Terayama et al., 2005). Moreover, high levels of KLK6 were observed in the sampled CSF and serum of patients suffering from progressive MS (Scarisbrick et al., 2008; LO Hebb et al., 2010).

Multiple Sclerosis and Autophagy

Autophagy is another major molecular mechanism implicated in the pathogenesis of MS. Autophagy is responsible for the breakdown and efficient utilization of damaged cellular components to maintain optimal cellular homeostasis (Parzych et al., 2014). Autophagy is a complex molecular mechanism that is responsible for maintaining cellular homeostasis, but when this molecular mechanism is compromised, it becomes harmful to the cells, especially to highly differentiated cells such as neurons (Parzych et al., 2014). This double-edged nature of autophagy rendered it one of the most investigated molecular mechanisms implicated in MS pathogenesis (Misrielal et al., 2020). Impaired expression of the autophagy genes occurs in T lymphocytes and tissues of MS patients and EAE animal models (Feng et al., 2017). Autophagy is also a critical regulator of both the adaptive and the innate immune responses, one of the basic and most concrete mechanisms involved in MS pathology (Levine et al., 2011).

Autophagosome formation is a fundamental step in autophagy, regulated by Beclin1 and Microtubule-associated protein 1A/1B-light chain 3 (LC3) genes (Tanida, 2010; Lee et al., 2017). The assessment of Beclin1 and LC3 expression levels is a widely utilized approach to indicate if autophagy is in its optimal status or has been compromised (Sahni et al., 2014; Lee et al., 2016). Beclin1 was the earliest gene described in mammalian autophagy (Wirawan et al., 2012). Interplay between Beclin1, B-cell lymphoma 2 (BCL-2), and other proteins mediate autophagy levels (Liang et al., 1998). Competitive binding of proteins to Beclin1 or BCL-2 can disturb or reinforce the Beclin1 separation from BCL-2, being the required step to initiate autophagy (Tran et al., 2021).

Multiple Sclerosis and Mitochondrial Homeostasis

Mitochondrial dynamics is a term that identifies the continuous fission and fusion, and the balance between these two processes ensures the preservation of mitochondrial integrity (Tilokani et al., 2018). Mitochondrial fission is the cleavage of one mitochondrion into two separate mitochondria, while mitochondrial fusion is the merging of two separate mitochondria to produce one fused mitochondrion (Tilokani et al., 2018). To maintain balanced mitochondrial fusion and fission, proteins such as mitofusin 1 and 2 (MFN1 and MFN2) are essential, as they mediate the fusion of mitochondria, whereas proteins such as dynamin-related protein 1 (Drp1) regulate the mitochondrial fission (Frank et al., 2001; Wang et al., 2019). Disrupted Drp1 expression leads to unregulated mitochondrial fission and fragmentation, leading to axonal and neuronal loss (Cho et al., 2009). Inhibition of Drp1 prevents excessive mitochondrial fragmentation and, therefore, attenuates EAE progression in animal models (Luo et al., 2017). In contrast, the MFN2 gene is a key generator of healthy mitochondria in neurons; its inhibition will lead to the loss of mitochondria, initiating autophagy and apoptosis, leading to neuronal loss (de Oliveira et al., 2021). Moreover, inhibition of MFN2 in human spinal motor neurons is responsible for the loss of axonal integrity as it impairs mitochondrial transport along axons, impairing the critical stable energy flux into these axons (Mou et al., 2021). Therefore, disruption in mitochondrial dynamics and mitochondrial dysfunction are implicated in the pathogenesis of MS and EAE (Campbell et al., 2014; Sadeghian et al., 2016).

Another process that preserves mitochondrial integrity is mitochondrial biogenesis, the process that generates new mitochondria from the growth and division of pre-existing ones (Ploumi et al., 2017; Li et al., 2017). Specific nuclear transcription factors mediating the expression of the genes that encode the mitochondrial proteins are implicated in mitochondrial biogenesis. The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), nuclear respiratory factors (NRF1 and NRF2) are critical elements in the assortment of components that regulate mitochondrial biogenesis (Ploumi et al., 2017). Moreover, mitochondrial biogenesis is mediated via mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B1 (TFB1M), and B2 (TFB2M) in addition to mitochondrial DNA (mtDNA) copy number (Ploumi et al., 2017; Song et al., 2023). The mitochondrial biogenesis gene expression profile, including PGC-1α, TFAM, and NRF1, as well as mtDNA copy number, exhibit a distinct decline in MS patients, which indicates that reduced expression of those mitochondrial biogenesis genes makes an integral implication in the pathogenesis of MS (Campbell et al., 2011; Witte et al., 2014; Barcelos et al., 2019; Song et al., 2023; Wang et al., 2024).

Multiple Sclerosis and Oxidative Stress

Since neurons have a specifically high energy demand, they utilize a high amount of oxygen, which induces the excessive production and release of reactive oxygen species (ROS), disabling the cell's machinery to neutralize and clear these ROS, eventually leading to uncontrolled oxidative stress (Watts et al., 2018). Oxidative stress has been considered an essential contributor to neurodegeneration (Watts et al., 2018). Also, it is responsible for myelin destruction and the disruption of BBB integrity, followed by infiltration of immune cells into the CNS, which are distinct hallmarks of the pathogenesis of MS (Lehner et al., 2011). Thus, its implication in MS pathogenesis is the main target of numerous therapeutic approaches (Fetisova et al., 2017). The use of antioxidants protects neurons against oxidative damage, promotes remyelination of the oligodendrocytes, and hence hinders the progression of MS lesions and induces remission of MS symptoms (Fetisova et al., 2017; Pegoretti et al., 2020; Zha et al., 2022).

Nitric oxide (NO) is a viable marker of oxidative stress (Bryan et al., 2004). It is implicated in many biological functions like neurotransmission, immune response, vasodilation, and platelet aggregation (Schlossmann et al., 2003; Cosby et al., 2003). Thus, NO is a main culprit in several pathological conditions, including NDs (Lundberg et al., 2008; Knott et al., 2009). It is produced by nitric oxide synthase (NOS) throughout the conversion of L-arginine to L-citrulline (Coleman, 2001). In the incidence of inflammation within the brain, glial cells produce excessive amounts of NO as an inflammatory response (Olivera et al., 2016). This abnormal increase in the levels of NO aggravates neuroinflammation and induces neuronal death (Olivera et al., 2016; Liy et al., 2021). The consequence is an additional trigger for NOS expression, generating even more NO and creating this vicious cycle of neurodegeneration (Subedi et al., 2021). Notably, there is a strong correlation between the high levels of nitric oxide end products (NOx) and the progression severity of MS (Calabrese et al., 2002).

Malondialdehyde (MDA) is a final product of lipid peroxidation and a viable marker of oxidative stress (Del Rio et al., 2005). The increased production of ROS is responsible for MDA upregulation (Gaweł et al., 2004). MDA is a cytotoxic molecule that has detrimental effects on various cellular mechanisms and has been involved in several pathogenic disorders, including NDs (Taso et al., 2019; Tofighi et al., 2021; Cordiano et al., 2023). MS patients have significantly elevated serum MDA levels, especially during their relapse periods compared to the remission periods, which illustrates a direct correlation between the MDA level and the progression of the disease (Ghonimi et al., 2021).

Treatment of Multiple Sclerosis

The Food and Drug Administration (FDA) agency has officially validated 15 medications such as alemtuzumab, dimethyl fumarate (Tecfidera), fingolimod (Gilenya), ocrelizumab, mitoxantrone, natalizumab, peginterferon beta-1a, teriflunomide (Aubagio), glatiramer acetate (Copaxone), IFNβ-1a and IFNβ-1b to hinder the progression of MS and reverse its complications (English et al., 2015; Li et al., 2020). Disease Modifying Treatments (DMTs) can also reduce the rate of relapses in relapsing remitting multiple sclerosis (RRMS) patients and slow the progression of MS, especially when the treatment is administered early (Loma et al., 2011; Comi et al., 2012; Noyes et al., 2013).

The major problems with the existing medications that treat MS are their adverse complications in addition to their extremely high cost (Hartung et al., 2015; Rafiee Zadeh et al., 2019). For instance, in the case of glatiramer acetate, commercially known as Copaxone, which is a first-line disease-modifying agent utilized for the treatment of patients with relapsing-remitting MS (RRMS). Serious adverse effects have been reported among MS patients receiving Copaxone. Such effects include injection site reactions or symptoms of a systemic immediate post-injection reaction including flushing, chest pain, palpitations, anxiety, dyspnea, tachycardia and throat constriction (Ziemssen et al., 2008; Caporro et al., 2014). Other complications have been also reported in MS patients treated with alemtuzumab. These complications include infusion-related symptoms, cytokine storm, increased risk of autoimmune diseases and increased risk of infections (Gross et al., 2015). About 20 to 30% of alemtuzumab treated patients have also reported problems in the thyroid gland and Graves' disease and hypothyroidism have been linked to the autoimmune complications of alemtuzumab (Coles et al., 1999; Mahzari et al., 2015). Many MS patients receiving dimethyl fumarate experience gastrointestinal irritation and flushing during treatment which pressure some of the patients to discontinue the treatment as the discomfort becomes unbearable (Phillips et al., 2014; Xu et al., 2015).

The other major obstacle that MS patients face is that these medications are extremely expensive. Studies investigating the prices of these medications in the American pharmaceutical market stated that first-generation DMTs, originally costing $8,000 to $11,000 lately cost $72,744 per year and these prices have been facing even further escalation in recent years (Hartung et al., 2015; Schauf et al., 2023).

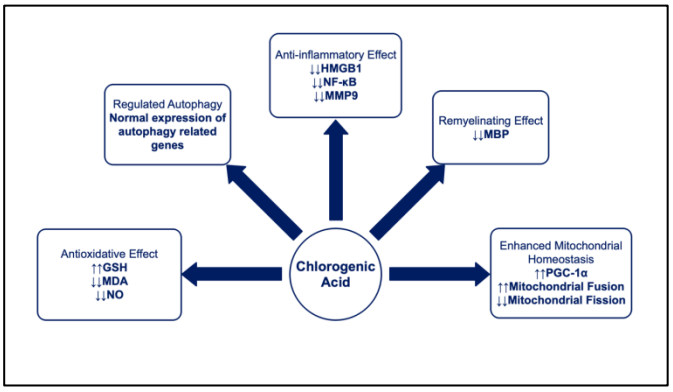
The complications of these medications and the continuous rising in their pieces are what compelled researchers to explore the availability of lower-cost therapies that may considerably decrease the economic burden on these patients and the health care systems. Several studies aimed to exploit the neuroinflammatory and neuroprotective potential of countless natural products in attempts to implicate them in treating the symptoms of NDs and explore their potential ability to attenuate the progression of these NDs (Mohd Sairazi et al., 2020; Sharifi-Rad et al., 2020; Chen et al., 2021; Lu et al., 2022).

Chlorogenic Acid

Chlorogenic acid (CA), also referred to as 5-*O*-caffeoylquinic acid (5-CQA), is an abundant highly functional polyphenolic compound found in different types of coffee beans (Farah et al., 2006). Green coffee beans are the richest with CA as they contain 5–14% of CA but this percentage is significantly reduced after roasting (Farah et al., 2006; Moon et al., 2009).

Supplements of CA have been used as over-the-counter metabolic boosters and weight loss inducers (Pepper, 2013).

Besides its role as a promising natural weight loss supplement, CA lowers blood glucose levels and attenuates insulin resistance (Roshan et al., 2018). It ameliorates inflammatory conditions as it targets multiple inflammatory pathways, and it has diminished drug resistance (Wang et al., 2022; Lemos et al., 2022; Feng et al., 2023). It possesses several cardiovascular and neurological protective properties (Wang et al., 2020; Zheng et al., 2022). Moreover, studies have provided concrete evidence of the promising potential of CA to treat brain and spinal cord injuries (Chen et al., 2018; Zheng et al., 2022). These neuroprotective effects were exerted by regulating oxidative stress related pathways as well as mediating various anti-inflammatory pathways in the brain and spinal cord (Figure2) (Rebai et al., 2017; Chen et al., 2018). Numerous studies have also illustrated the neuroprotective effects of CA and its ability to improve cerebral ischemia-reperfusion (CI/R) injury in rats (Kumar et al., 2019; Liu et al., 2020; Li et al., 2023).



Figure(2):A diagrammatic presentation of the neuroprotective, anti-inflammatory and antioxidative effects of chlorogenic acid. *HMGB1: High Mobility Group Box Protein 1, NF-κB: Nuclear Factor kappa B, MMP9: Matrix Metalloproteinase 9, MBP: Myelin Basic Protein, PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha, GSH: Glutathione, MDA: Malondialdehyde, and NO: Nitric Oxide.*

Chlorogenic Acid and Neuroinflammation

CA exerts its neuroprotective capacity by blocking the signaling pathways of neuroinflammatory mediators such as HMGB1 and NF-κB (Huang et al., 2023; Li et al., 2023). CA alleviates hepatic ischemia–reperfusion injury (HIRI) by suppressing the active release of HMGB1 in rats (Li et al., 2023). This study also found that CA can protect against HIRI by alleviating the inflammatory response mediated by the HMGB1/TLR-4/NF-κB axis (Li et al., 2023). Similarly, in a sepsis model, CA protects mice from sepsis by blocking the release of HMGB1 (Lee et al., 2012). Additionally, CA prevents the nuclear translocation of NF-κB, blocking its subsequent target gene binding and inhibiting its activation (Yu et al., 2021; Shah et al., 2022; Orhan et al., 2024). Another study found that CA inhibits the NF-κB pathway and alleviates the intestinal damage induced by chronic stress in rats (Zhao et al., 2023). A study also found that CA reduced spinal cord injury and actively suppressed the accompanied cascades of neuroinflammation by regulating the NF-κB signaling pathways (Chen et al., 2018). Further studies illustrated the aforementioned neuroprotective effects of CA (Heitman et al., 2017; Liu et al., 2020; Xiong et al., 2023). *In vivo* data also demonstrated that CA treatment improves the survival of dopaminergic neurons and inhibits lipopolysaccharide (LPS)-induced microglial activation (Shen et al., 2012).

Another inflammatory mediator that CA targets as it mediates its anti-inflammatory activity is MMP9. A study aimed to investigate CA as a candidate chemo-preventive agent in hepatocellular carcinoma demonstrated that CA suppressed MMP9, which prevented the disintegration of the extracellular matrix and it suppressed the invasion and proliferation of cancerous cells and attenuated metastasis (Liu et al., 2020). Studies that explored the neuroprotective effects of CA found that CA ameliorates brain damage and edema by inhibiting MMP9 in a rat model of focal cerebral ischemia (Lee et al., 2012). Another study found that CA preserved the integrity of BBB by suppressing the expression of MMP9 in a mouse model of intracerebral hemorrhage as it subsequently attenuated the neurological impairments and reduced brain water content (Liu et al., 2022).

Chlorogenic Acid and Demyelination

As mentioned earlier, OLs are the myelin forming cells in the CNS, are the main target in demyelinating neuroinflammatory diseases such as MS. So, studies have been relentless to induce remyelinating machineries and to protect OLs. A study aimed to investigate the effects of CA in M03-13, an immortalized human OL cell line found that CA induces a blockade of proliferation, driving cells to differentiation, generating increased mRNA levels of MBP and proteolipid protein (PLP), which are major markers of mature OLs. The findings of this study emphasized the great beneficial potential of CA in reversing the demyelination induced by MS (La Rosa et al., 2023).

Chlorogenic Acid and Autophagy

In neurons, the autophagy process is critical for mitochondrial function. Dysregulation in autophagy contributes to the accumulation of damaged mitochondria and other dysfunctional organelles, exacerbation of oxidative stress, neuroinflammation, and eventually neuronal cell death in NDs. Elevated autophagy biomarkers positively correlate with aggravated axonal damage and MS progression as over-activation of autophagy is implicated in detrimental neurological consequences (Li et al., 2019). CA demonstrated autophagy-suppressing effects in several disease models, namely non-alcoholic fatty liver disease (NAFLD) (Yan et al., 2018) and Alzheimer's disease (Gao et al., 2020). The study evaluating the effects of CA on NAFLD model, demonstrated that CA treatment attenuated the liver injury induced by high fat diet, and it inhibited autophagy and ameliorated insulin resistance in a rat model of NAFLD (Yan et al., 2018). Another study found that the neuroprotective effects of CA are attributed to its role in the inhibition of neuronal cell apoptosis and autophagy induced by neurotoxicity as it can actively reverse such damage when it occurs (Shi et al., 2019).

Chlorogenic Acid and Mitochondrial Homeostasis

Given the importance of mitochondria in neuronal cells, mitochondrial homeostasis is an important aspect that should be studied in any study related to CNS disorders, including MS. Mitochondrial homeostasis is the coordinated equilibrium between different mitochondrial processing, including mitophagy, mitochondrial fission and fusion, and mitochondrial biogenesis (Bustamante-Barrientos et al., 2023). Impaired mitochondrial dynamics are implicated in most NDs (Antonucci et al., 2021). Similar to autophagy, the over-activation of mitophagy in MS animal model aggravates the pathological complications of the disease (Cossu et al., 2022). In addition to impaired mitophagy, anomalies in mitochondrial biogenesis are implicated in MS (Wang et al., 2024). A study that explored the various protective effects of CA against kainic acid-induced seizures and neuronal damage in rats found that CA prevents kainic acid-induced alterations in autophagy and mitophagy parameters (Pai et al., 2023). This study illustrated that CA-induced upregulation of PGC-1α prevented kainic acid-induced neuronal damage in rats as it subsequently alleviated the kainic acid-induced mitochondrial damage and preserved the hippocampal mitochondrial integrity.

Chlorogenic Acid and Oxidative Stress

CA is also a potent antioxidant (Liang et al., 2015; Bao et al., 2018). CA can attenuate hydrogen peroxide-induced oxidative damage. In addition, CA treatment improves mitochondrial membrane potential and inhibits free radical formation (Li et al., 2023). A study has shown that CA increased antioxidant enzymes activities, along with higher GSH contents, as CA improved the cellular antioxidant defense in epileptic mice. These results were associated with lowered MDA and NO levels (Althagafi, 2024).

Studies have aimed to explicitly illustrate the antioxidant activity of CA. For instance, a study investigated the role of CA in protection against the induction of oxidative stress in the CNS following exposure to cadmium (Cd) found that the pretreatment of rats with CA prior to Cd exposure significantly restored the depleted levels of GSH, and attenuated Cd-induced MDA levels in brain tissue (Hao et al., 2015). Another study using an animal model of Alzheimer's disease, has found that CA decreased the MDA level in both the frontal cortex and the hippocampus (Kwon et al., 2010). This antioxidative activity of CA was attributed to its affinity to reduce lipid peroxidation in addition to reducing free radical scavenging activity (Kwon et al., 2010).

Conclusion and Future Perspectives

Chlorogenic acid is an innovative agent with numerous potential pharmacological effects. To date, its ability to target neuro-inflammatory processes during MS pathology has been proven in preclinical studies utilizing an animal model of MS. One of the most important characteristics proving the potential of chlorogenic acid is its multifaceted mechanism of action, which is closely related to the pathomechanism of MS.

Considering that MS is not only chronic and progressive but also heterogeneous, it would be interesting to explore further studies where chlorogenic acid could be tested on an innovative MS-like model characterized by both neurodegenerative features and accumulation in diverse endophenotypes. Such studies could be conducted through collaboration between neuropathologists and laboratory scientists with extensive research experience in neural degeneration.

References

1. Ahmed, Mumdooh AM, Vladimir V Bamm, George Harauz, and Vladimir Ladizhansky. 2010. 'Solid-state NMR spectroscopy of membrane-associated myelin basic protein—conformation and dynamics of an immunodominant epitope', *Biophysical journal*, 99: 1247-55.
2. Aleksandr, Shenfeld, and Galkin Alexey. 2022. 'Role of the MBP protein in myelin formation and degradation in the brain', *Biological Communications*, 67: 127-38.
3. Althagafi, Hussam A. 2024. 'Neuroprotective role of chlorogenic acid against hippocampal neuroinflammation, oxidative stress, and apoptosis following acute seizures induced by pentylenetetrazole', *Metabolic Brain Disease*, 39: 1307-21.
4. Andersson, Ulf, Huan Yang, and Helena Harris. 2018. 'Extracellular HMGB1 as a therapeutic target in inflammatory diseases', *Expert opinion on therapeutic targets*, 22: 263-77.
5. Antonucci, Salvatore, Fabio Di Lisa, and Nina Kaludercic. 2021. 'Mitochondrial reactive oxygen species in physiology and disease', *Cell Calcium*, 94: 102344.
6. Baecher-Allan, Clare, Belinda J. Kaskow, and Howard L. Weiner. 2018. 'Multiple Sclerosis: Mechanisms and Immunotherapy', *Neuron*, 97: 742-68.
7. Bao, Liping, Jushuang Li, Dongqing Zha, Lian Zhang, Ping Gao, Tao Yao, and Xiaoyan Wu. 2018. 'Chlorogenic acid prevents diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF-κB pathways', *International immunopharmacology*, 54: 245-53.
8. Barcelos, I. P., R. M. Troxell, and J. S. Graves. 2019. 'Mitochondrial Dysfunction and Multiple Sclerosis', *Biology (Basel)*, 8.
9. Bryan, Nathan S, Tienush Rassaf, Ronald E Maloney, Cynthia M Rodriguez, Fumito Saijo, Juan R Rodriguez, and Martin Feelisch. 2004. 'Cellular targets and mechanisms of nitros (yl) ation: an insight into their nature and kinetics in vivo', *Proceedings of the National Academy of Sciences*, 101: 4308-13.
10. Bustamante-Barrientos, Felipe A, Noymar Luque-Campos, María Jesús Araya, Eliana Lara-Barba, Javiera de Solminihac, Carolina Pradenas, Luis Molina, Yeimi Herrera-Luna, Yildy Utreras-Mendoza, and Roberto Elizondo-Vega. 2023. 'Mitochondrial dysfunction in neurodegenerative disorders: Potential therapeutic

application of mitochondrial transfer to central nervous system-residing cells', *Journal of Translational Medicine*, 21: 613.

11. Calabrese, Vittorio, Giovanni Scapagnini, Agrippino Ravagna, Rita Bella, Roberta Foresti, Timothy E Bates, Anna-Maria Giuffrida Stella, and Giovanni Pennisi. 2002. 'Nitric oxide synthase is present in the cerebrospinal fluid of patients with active multiple sclerosis and is associated with increases in cerebrospinal fluid protein nitrotyrosine and S-nitrosothiols and with changes in glutathione levels', *Journal of neuroscience research*, 70: 580-87.
12. Campbell, Graham R, Joseph T Worrall, and Don J Mahad. 2014. 'The central role of mitochondria in axonal degeneration in multiple sclerosis', *Multiple Sclerosis Journal*, 20: 1806-13.
13. Campbell, Graham R, Iryna Ziabreva, Amy K Reeve, Kim J Krishnan, Richard Reynolds, Owen Howell, Hans Lassmann, Doug M Turnbull, and Don J Mahad. 2011. 'Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis', *Annals of Neurology*, 69: 481-92.
14. Caporro, Matteo, Giulio Disanto, Claudio Gobbi, and Chiara Zecca. 2014. 'Two decades of subcutaneous glatiramer acetate injection: current role of the standard dose, and new high-dose low-frequency glatiramer acetate in relapsing–remitting multiple sclerosis treatment', *Patient preference and adherence*: 1123-34.
15. Chang, Ansi, Wallace W Tourtellotte, Richard Rudick, and Bruce D Trapp. 2002. 'Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis', *New England Journal of Medicine*, 346: 165-73.
16. Chen, Dayong, Dan Pan, Shaolong Tang, Zhihong Tan, Yanan Zhang, Yunfeng Fu, Guohua Lü, and Qinghua Huang. 2018. 'Administration of chlorogenic acid alleviates spinal cord injury via TLR4/NF‐κB and p38 signaling pathway anti‐inflammatory activity', *Molecular medicine reports*, 17: 1340-46.
17. Chen, Xin, Joshua Drew, Wren Berney, and Wei Lei. 2021. 'Neuroprotective natural products for Alzheimer's disease', *Cells*, 10: 1309.
18. Cho, Dong-Hyung, Tomohiro Nakamura, Jianguo Fang, Piotr Cieplak, Adam Godzik, Zezong Gu, and Stuart A Lipton. 2009. 'S-nitrosylation of Drp1 mediates β-amyloid-related mitochondrial fission and neuronal injury', *Science*, 324: 102-05.
19. Choonara, Y. E., V. Pillay, L. C. Du Toit, G. Modi, D. Naidoo, V. M. K. Ndesendo, and S. R. Sibambo. 2009. 'Trends in the molecular pathogenesis and clinical therapeutics of common neurodegenerative disorders', *Int J Mol Sci*, 10: 2510-57.
20. Coleman, John W. 2001. 'Nitric oxide in immunity and inflammation', *International immunopharmacology*, 1: 1397-406.
21. Coles, Alasdair J, Mark Wing, Sheila Smith, Francesca Coraddu, Sandra Greer, Craig Taylor, Anthony Weetman, Geoff Hale, V Krishna Chatterjee, and Herman Waldmann. 1999. 'Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis', *The Lancet*, 354: 1691-95.
22. Comi, Giancarlo, Nicola De Stefano, Mark S Freedman, Frederik Barkhof, Chris H Polman, Bernard MJ Uitdehaag, Florence Casset-Semanaz, Brian Hennessy, Margaretha Stam Moraga, and Sanda Rocak. 2012. 'Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial', *The Lancet Neurology*, 11: 33-41.
23. Confavreux, Christian, Sandra Vukusic, Thibault Moreau, and Patrice Adeleine. 2000. 'Relapses and Progression of Disability in Multiple Sclerosis', *New England Journal of Medicine*, 343: 1430-38.
24. Cordiano, Raffaele, Mario Di Gioacchino, Rocco Mangifesta, Claudia Panzera, Sebastiano Gangemi, and Paola Lucia Minciullo. 2023. 'Malondialdehyde as a potential oxidative stress marker for allergy-oriented diseases: an update', *Molecules*, 28: 5979.
25. Cosby, Kenyatta, Kristine S Partovi, Jack H Crawford, Rakesh P Patel, Christopher D Reiter, Sabrina Martyr, Benjamin K Yang, Myron A Waclawiw, Gloria Zalos, and Xiuli Xu. 2003. 'Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation', *Nature Medicine*, 9: 1498-505.
26. Cossu, Davide, Kazumasa Yokoyama, Shigeto Sato, Sachiko Noda, Tamami Sakanishi, Leonardo Antonio Sechi, and Nobutaka Hattori. 2022. 'Age related immune modulation of experimental autoimmune encephalomyelitis in PINK1 knockout mice', *Frontiers in Immunology*, 13: 1036680.
27. de Oliveira, Lilian Gomes, Yan de Souza Angelo, Antonio H Iglesias, and Jean Pierre Schatzmann Peron. 2021. 'Unraveling the link between mitochondrial dynamics and neuroinflammation', *Frontiers in Immunology*, 12: 624919.
28. Del Rio, Daniele, Amanda J Stewart, and Nicoletta Pellegrini. 2005. 'A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress', *Nutrition, metabolism and cardiovascular diseases*, 15: 316-28.
29. Duncan, Greg J, Tyrell J Simkins, and Ben Emery. 2021. 'Neuron-oligodendrocyte interactions in the structure and

integrity of axons', *Frontiers in Cell and Developmental Biology*, 9: 653101.

30. Duncan, Ian D, Abigail B Radcliff, Moones Heidari, Grahame Kidd, Benjamin K August, and Lauren A Wierenga. 2018. 'The adult oligodendrocyte can participate in remyelination', *Proceedings of the National Academy of Sciences*, 115: E11807-E16.
31. Eggert, Martin, Robert Goertsches, Ulrike Seeck, Silvia Dilk, Gunther Neeck, and Uwe K Zettl. 2008. 'Changes in the activation level of NF-kappa B in lymphocytes of MS patients during glucocorticoid pulse therapy', *Journal of the neurological sciences*, 264: 145-50.
32. English, Clayton, and Joseph J Aloi. 2015. 'New FDA-approved disease-modifying therapies for multiple sclerosis', *Clinical therapeutics*, 37: 691-715.
33. Evans, Charity, Sarah-Gabrielle Beland, Sophie Kulaga, Christina Wolfson, Elaine Kingwell, James Marriott, Marcus Koch, Naila Makhani, Sarah Morrow, and John Fisk. 2013. 'Incidence and prevalence of multiple sclerosis in the Americas: a systematic review', *Neuroepidemiology*, 40: 195-210.
34. Farah, Adriana, and Carmen Marino Donangelo. 2006. 'Phenolic compounds in coffee', *Brazilian journal of plant physiology*, 18: 23-36.
35. Feigin, Valery L, Amanuel Alemu Abajobir, Kalkidan Hassen Abate, Foad Abd-Allah, Abdishakur M Abdulle, Semaw Ferede Abera, Gebre Yitayih Abyu, Muktar Beshir Ahmed, Amani Nidhal Aichour, and Ibtihel Aichour. 2017. 'Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015', *The Lancet Neurology*, 16: 877-97.
36. Feng, Shiyuan, Yihao Zhang, Shaodong Fu, Zhi Li, Jinqiu Zhang, Yuanyuan Xu, Xiangan Han, and Jinfeng Miao. 2023. 'Application of Chlorogenic acid as a substitute for antibiotics in Multidrug-resistant Escherichia coli-induced mastitis', *International immunopharmacology*, 114: 109536.
37. Feng, Xuedan, Huiqing Hou, Yueli Zou, and Li Guo. 2017. 'Defective autophagy is associated with neuronal injury in a mouse model of multiple sclerosis', *Bosnian Journal of Basic Medical Sciences*, 17: 95.
38. Ferrer, I. 2018. 'Oligodendrogliopathy in neurodegenerative diseases with abnormal protein aggregates: The forgotten partner', *Prog Neurobiol*, 169: 24-54.
39. Fetisova, Elena, Boris Chernyak, Galina Korshunova, Maria Muntyan, and Vladimir Skulachev. 2017. 'Mitochondria-targeted antioxidants as a prospective therapeutic strategy for multiple sclerosis', *Current Medicinal Chemistry*, 24: 2086-114.
40. Frank, Stephan, Brigitte Gaume, Elke S Bergmann-Leitner, Wolfgang W Leitner, Everett G Robert, Frédéric Catez, Carolyn L Smith, and Richard J Youle. 2001. 'The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis', *Developmental cell*, 1: 515-25.
41. Franklin, Robin JM. 2002. 'Why does remyelination fail in multiple sclerosis?', *Nature Reviews Neuroscience*, 3: 705-14.
42. Frischer, Josa M, Stephen D Weigand, Yong Guo, Nilufer Kale, Joseph E Parisi, Istvan Pirko, Jay Mandrekar, Stephan Bramow, Imke Metz, and Wolfgang Brück. 2015. 'Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque', *Annals of Neurology*, 78: 710-21.
43. Funfschilling, U, L Supplie, D Mahad, S Boretius, A Saab, J Edgar, Kassmann CM Brinkmann Bg, Mobius W Tzvetanova Id, and F Diaz. 2012. 'Meijr d, Suter U, Hamprecht B, Sereda MW, Moraes CT, Frahm J, Goebbels S, Nave KA. glycolytic oligodendrocytes maintain myelin and long-term axonal integrity', *Nature*, 485: 517-21.
44. Gandhi, R., A. Laroni, and H. L. Weiner. 2010. 'Role of the innate immune system in the pathogenesis of multiple sclerosis', *J Neuroimmunol*, 221: 7-14.
45. Gao, Lijuan, Xiaoqiong Li, Shi Meng, Tengyun Ma, Lihong Wan, and Shijun Xu. 2020. 'Chlorogenic acid alleviates Aβ25-35-induced autophagy and cognitive impairment via the mTOR/TFEB signaling pathway', *Drug design, development and therapy*: 1705-16.
46. Gaweł, S., M. Wardas, E. Niedworok, and P. Wardas. 2004. '[Malondialdehyde (MDA) as a lipid peroxidation marker]', *Wiad Lek*, 57: 453-5.
47. Ghonimi, Nesma AM, Khaled A Elsharkawi, Doaa SM Khyal, and Alaa A Abdelghani. 2021. 'Serum malondialdehyde as a lipid peroxidation marker in multiple sclerosis patients and its relation to disease characteristics', *Multiple sclerosis and related disorders*, 51: 102941.
48. Gross, Robert H, and Stephen Krieger. 2015. 'Alemtuzumab in multiple sclerosis: an update', *Neurodegenerative Disease Management*, 5: 225-32.
49. Gruchot, Joel, Vivien Weyers, Peter Göttle, Moritz Förster, Hans-Peter Hartung, Patrick Küry, and David Kremer. 2019. 'The molecular basis for remyelination failure in multiple sclerosis', *Cells*, 8: 825.
50. Hao, Mao-Lin, Ning Pan, Qing-Hua Zhang, and Xiao-Hong Wang. 2015. 'Therapeutic efficacy of chlorogenic acid on cadmium-induced oxidative neuropathy in a murine model', *Experimental and therapeutic medicine*, 9: 1887-94.

51. Hartung, Daniel M, Dennis N Bourdette, Sharia M Ahmed, and Ruth H Whitham. 2015. 'The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: too big to fail?', *Neurology*, 84: 2185-92.
52. Hayden, Matthew S, and Sankar Ghosh. 2008. 'Shared principles in NF-κB signaling', *Cell*, 132: 344-62.
53. Heitman, Erin, and Donald K Ingram. 2017. 'Cognitive and neuroprotective effects of chlorogenic acid', *Nutritional Neuroscience*, 20: 32-39.
54. Henderson, Andrew P. D., Michael H. Barnett, John D. E. Parratt, and John W. Prineas. 2009. 'Multiple sclerosis: Distribution of inflammatory cells in newly forming lesions', *Annals of Neurology*, 66: 739-53.
55. Huang, J., M. Xie, L. He, X. Song, and T. Cao. 2023. 'Chlorogenic acid: a review on its mechanisms of anti-inflammation, disease treatment, and related delivery systems', *Front Pharmacol*, 14: 1218015.
56. Keirstead, Hans S, and William F Blakemore. 1997. 'Identification of post-mitotic oligodendrocytes incapable of remyelination within the demyelinated adult spinal cord', *Journal of Neuropathology & Experimental Neurology*, 56: 1191-201.
57. Knott, Andrew B, and Ella Bossy-Wetzel. 2009. 'Nitric oxide in health and disease of the nervous system', *Antioxid Redox Signal*, 11: 541-53.
58. Kumar, Gaurav, Sumedha Mukherjee, Pankaj Paliwal, Saumitra Sen Singh, Hareram Birla, Surya Pratap Singh, Sairam Krishnamurthy, and Ranjana Patnaik. 2019. 'Neuroprotective effect of chlorogenic acid in global cerebral ischemia-reperfusion rat model', *Naunyn-Schmiedeberg's Archives of Pharmacology*, 392: 1293-309.
59. Kwon, Seung-Hwan, Ha-Kyung Lee, Ji-Ah Kim, Sa-Ik Hong, Hyoung-Chun Kim, Tae-Hyung Jo, Young-In Park, Chong-Kil Lee, Yong-Bin Kim, and Seok-Yong Lee. 2010. 'Neuroprotective effects of chlorogenic acid on scopolamine-induced amnesia via anti-acetylcholinesterase and anti-oxidative activities in mice', *European journal of pharmacology*, 649: 210-17.
60. La Rosa, Giuliana, Concetta Sozio, Luca Pipicelli, Maddalena Raia, Anna Palmiero, Mariarosaria Santillo, and Simona Damiano. 2023. 'Antioxidant, Anti-Inflammatory and Pro-Differentiative Effects of Chlorogenic Acid on M03-13 Human Oligodendrocyte-like Cells', *Int J Mol Sci*, 24: 16731.
61. Lee, Chan-Ho, Seong-Jin Yoon, and Sun-Mee Lee. 2012. 'Chlorogenic acid attenuates high mobility group box 1 (HMGB1) and enhances host defense mechanisms in murine sepsis', *Molecular Medicine*, 18: 1437-48.
62. Lee, Kyungjin, Jeong-Sook Lee, Hyeung-Jin Jang, Sung-Moo Kim, Mun Seog Chang, Si Hyung Park, Kwan Su Kim, Jinhyun Bae, Jae-Woo Park, and Bumjun Lee. 2012. 'Chlorogenic acid ameliorates brain damage and edema by inhibiting matrix metalloproteinase-2 and 9 in a rat model of focal cerebral ischemia', *European journal of pharmacology*, 689: 89-95.
63. Lee, You-Kyung, and Jin-A Lee. 2016. 'Role of the mammalian ATG8/LC3 family in autophagy: differential and compensatory roles in the spatiotemporal regulation of autophagy', *BMB reports*, 49: 424.
64. Lee, You-Kyung, Yong-Woo Jun, Ha-Eun Choi, Yang Hoon Huh, Bong-Kiun Kaang, Deok-Jin Jang, and Jin-A Lee. 2017. 'Development of LC3/GABARAP sensors containing a LIR and a hydrophobic domain to monitor autophagy', *The EMBO Journal*, 36: 1100-16-16.
65. Lee, Youngjin, Brett M Morrison, Yun Li, Sylvain Lengacher, Mohamed H Farah, Paul N Hoffman, Yiting Liu, Akivaga Tsingalia, Lin Jin, and Ping-Wu Zhang. 2012. 'Oligodendroglia metabolically support axons and contribute to neurodegeneration', *Nature*, 487: 443-48.
66. Lehner, C., R. Gehwolf, H. Tempfer, I. Krizbai, B. Hennig, H. C. Bauer, and H. Bauer. 2011. 'Oxidative stress and blood-brain barrier dysfunction under particular consideration of matrix metalloproteinases', *Antioxid Redox Signal*, 15: 1305-23.
67. Lemos, Mayara Fumiere, Nathacha de Andrade Salustriano, Mariana Merigueti de Souza Costa, Karla Lirio, Aymbiré Francisco Almeida da Fonseca, Henrique Poltronieri Pacheco, Denise Coutinho Endringer, Marcio Fronza, and Rodrigo Scherer. 2022. 'Chlorogenic acid and caffeine contents and anti-inflammatory and antioxidant activities of green beans of conilon and arabica coffees harvested with different degrees of maturation', *Journal of Saudi Chemical Society*, 26: 101467.
68. Levine, Beth, Noboru Mizushima, and Herbert W Virgin. 2011. 'Autophagy in immunity and inflammation', *Nature*, 469: 323-35.
69. Li, Huihui, Fengli Hu, Yanli Zhang, and Kai Li. 2020. 'Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing–remitting multiple sclerosis: a systematic review and network meta-analysis', *Journal of Neurology*, 267: 3489-98.
70. Li, Jiaxin, Hengju Ge, Yang Xu, Jiahong Xie, Naymul Karim, Fujie Yan, Jianling Mo, and Wei Chen. 2023. 'Chlorogenic acid alleviates oxidative damage in hepatocytes by regulating miR-199a-5p/GRP78 axis', *Food Bioscience*, 53: 102595.
71. Li, Kai, Zanjie Feng, Liusong Wang, Xuan Ma, Lei Wang, Kangwei Liu, Xin Geng, and Cijun Peng. 2023. 'Chlorogenic acid alleviates hepatic ischemia–reperfusion injury by inhibiting oxidative stress, inflammation, and mitochondria-mediated apoptosis in vivo and in vitro', *Inflammation*, 46: 1061-76.

72. Li, P Andy, Xiaolin Hou, and Shaocai Hao. 2017. 'Mitochondrial biogenesis in neurodegeneration', *Journal of neuroscience research*, 95: 2025-29.
73. Li, Qiutang, and Inder M Verma. 2002. 'NF-κB regulation in the immune system', *Nature Reviews Immunology*, 2: 725-34.
74. Li, Wenting, Jinghan Feng, Chong Gao, Meiling Wu, Qiaohui Du, Bun Tsoi, Qi Wang, Dan Yang, and Jiangang Shen. 2019. 'Nitration of Drp1 provokes mitophagy activation mediating neuronal injury in experimental autoimmune encephalomyelitis', *Free Radical Biology and Medicine*, 143: 70-83.
75. Liang, Ningjian, and David D Kitts. 2015. 'Role of chlorogenic acids in controlling oxidative and inflammatory stress conditions', *Nutrients*, 8: 16.
76. Liang, X. H., L. K. Kleeman, H. H. Jiang, G. Gordon, J. E. Goldman, G. Berry, B. Herman, and B. Levine. 1998. 'Protection against fatal Sindbis virus encephalitis by beclin, a novel Bcl-2-interacting protein', *J Virol*, 72: 8586-96.
77. Lindsey, J William, Sandeep K Agarwal, and Filemon K Tan. 2011. 'Gene expression changes in multiple sclerosis relapse suggest activation of T and non-T cells', *Molecular Medicine*, 17: 95-102.
78. Little, Sheila P, Eric P Dixon, Frank Norris, William Buckley, Gerald W Becker, Melvin Johnson, John R Dobbins, Tamara Wyrick, James R Miller, and Warren MacKellar. 1997. 'Zyme, a novel and potentially amyloidogenic enzyme cDNA isolated from Alzheimer's disease brain', *Journal of Biological Chemistry*, 272: 25135-42.
79. Liu, D., H. Wang, Y. Zhang, and Z. Zhang. 2020. 'Protective Effects of Chlorogenic Acid on Cerebral Ischemia/Reperfusion Injury Rats by Regulating Oxidative Stress-Related Nrf2 Pathway', *Drug Des Devel Ther*, 14: 51-60.
80. Liu, Dequan, Huilin Wang, Yangang Zhang, and Zhan Zhang. 2020. 'Protective effects of chlorogenic acid on cerebral ischemia/reperfusion injury rats by regulating oxidative stress-related Nrf2 pathway', *Drug design, development and therapy*: 51-60.
81. Liu, Y., Y. Feng, Y. Li, Y. Hu, Q. Zhang, Y. Huang, K. Shi, C. Ran, J. Hou, G. Zhou, and X. Wang. 2020. 'Chlorogenic Acid Decreases Malignant Characteristics of Hepatocellular Carcinoma Cells by Inhibiting DNMT1 Expression', *Front Pharmacol*, 11: 867.
82. Liu, Y., F. Wang, Z. Li, Y. Mu, V. W. Yong, and M. Xue. 2022. 'Neuroprotective Effects of Chlorogenic Acid in a Mouse Model of Intracerebral Hemorrhage Associated with Reduced Extracellular Matrix Metalloproteinase Inducer', *Biomolecules*, 12.
83. Liy, P. M., N. N. A. Puzi, S. Jose, and S. Vidyadaran. 2021. 'Nitric oxide modulation in neuroinflammation and the role of mesenchymal stem cells', *Exp Biol Med (Maywood)*, 246: 2399-406.
84. LO Hebb, Andrea, Virender Bhan, Alexander D Wishart, Craig S Moore, and George S Robertson. 2010. 'Human kallikrein 6 cerebrospinal levels are elevated in multiple sclerosis', *Current drug discovery technologies*, 7: 137-40.
85. Loma, Ingrid, and Rock Heyman. 2011. 'Multiple Sclerosis: Pathogenesis and Treatment', *Current Neuropharmacology*, 9: 409-16.
86. Lu, Changcheng, Shuhui Qu, Zhangfeng Zhong, Hua Luo, Si San Lei, Hai-Jing Zhong, Huanxing Su, Yitao Wang, and Cheong-Meng Chong. 2022. 'The effects of bioactive components from the rhizome of gastrodia elata blume (Tianma) on the characteristics of Parkinson's disease', *Frontiers in Pharmacology*, 13: 963327.
87. Lucchinetti, Claudia, and Reinhard Hohlfeld. 2009. *Multiple Sclerosis 3, Volume 34 E-Book: Blue Books of Neurology Series* (Elsevier Health Sciences).
88. Lundberg, Jon O, Eddie Weitzberg, and Mark T Gladwin. 2008. 'The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics', *Nature reviews Drug discovery*, 7: 156-67.
89. Luo, Fucheng, Karl Herrup, Xin Qi, and Yan Yang. 2017. 'Inhibition of Drp1 hyper-activation is protective in animal models of experimental multiple sclerosis', *Experimental neurology*, 292: 21-34.
90. Mahzari, Moeber, Amel Arnaout, and Mark S Freedman. 2015. 'Alemtuzumab induced thyroid disease in multiple sclerosis: a review and approach to management', *Canadian Journal of Neurological Sciences*, 42: 284-91.
91. Martinsen, Vebjørn, and Petri Kursula. 2022. 'Multiple sclerosis and myelin basic protein: insights into protein disorder and disease', *Amino Acids*, 54: 99-109.
92. Mc Guire, Conor, Marco Prinz, Rudi Beyaert, and Geert van Loo. 2013. 'Nuclear factor kappa B (NF-κB) in multiple sclerosis pathology', *Trends Mol Med*, 19 10: 604-13.
93. Min, Younjin, Kai Kristiansen, Joan M Boggs, Cynthia Husted, Joseph A Zasadzinski, and Jacob Israelachvili. 2009. 'Interaction forces and adhesion of supported myelin lipid bilayers modulated by myelin basic protein', *Proceedings of the National Academy of Sciences*, 106: 3154-59.
94. Misrielal, Chairi, Mario Mauthe, Fulvio Reggiori, and Bart JL Eggen. 2020. 'Autophagy in multiple sclerosis: two sides of the same coin', *Frontiers in cellular neuroscience*, 14: 603710.
95. Mitew, Stanislaw, Curtis M Hay, Haley Peckham, Junhua Xiao, Matthias Koenning, and Ben Emery. 2014.

'Mechanisms regulating the development of oligodendrocytes and central nervous system myelin', *Neuroscience*, 276: 29-47.

96. Mohd Sairazi, Nur Shafika, and KNS Sirajudeen. 2020. 'Natural products and their bioactive compounds: neuroprotective potentials against neurodegenerative diseases', *Evidence-Based Complementary and Alternative Medicine*, 2020.
97. Moon, Joon-Kwan, and Takayuki Shibamoto. 2009. 'Role of roasting conditions in the profile of volatile flavor chemicals formed from coffee beans', *Journal of Agricultural and Food Chemistry*, 57: 5823-31.
98. Mou, Y., J. Dein, Z. Chen, M. Jagdale, and X. J. Li. 2021. 'MFN2 Deficiency Impairs Mitochondrial Transport and Downregulates Motor Protein Expression in Human Spinal Motor Neurons', *Front Mol Neurosci*, 14: 727552.
99. Noyes, K., and B. Weinstock-Guttman. 2013. 'Impact of diagnosis and early treatment on the course of multiple sclerosis', *Am J Manag Care*, 19: s321-31.
100. Olivera, Gabriela C, Xiaoyuan Ren, Suman K Vodnala, Jun Lu, Lucia Coppo, Chaniya Leepiyasakulchai, Arne Holmgren, Krister Kristensson, and Martin E Rottenberg. 2016. 'Nitric oxide protects against infection-induced neuroinflammation by preserving the stability of the blood-brain barrier', *PLoS pathogens*, 12: e1005442.
101. Orhan, Semiha, Ruhi Turkmen, Hasan Huseyin Demirel, Murat Sırrı Akosman, Turkan Turkmen, and Fatma Fırat. 2024. 'Chlorogenic acid mitigates potassium dichromate-induced acute hepato-nephrotoxicity by attenuating the NF-κB signalling pathway', *Molecular Biology Reports*, 51: 798.
102. Pai, Ming-Shang, Kaw-Chen Wang, Kun-Chieh Yeh, and Su-Jane Wang. 2023. 'Stabilization of mitochondrial function by chlorogenic acid protects against kainic acid-induced seizures and neuronal cell death in rats', *European journal of pharmacology*, 961: 176197.
103. Parzych, K. R., and D. J. Klionsky. 2014. 'An overview of autophagy: morphology, mechanism, and regulation', *Antioxid Redox Signal*, 20: 460-73.
104. Paudel, Yam Nath, Efthalia Angelopoulou, KC Bhuvan, Christina Piperi, and Iekhsan Othman. 2019. 'High mobility group box 1 (HMGB1) protein in Multiple Sclerosis (MS): Mechanisms and therapeutic potential', *Life Sci*, 238: 116924.
105. Paudel, Yam Nath, Mohd Farooq Shaikh, Ayanabha Chakraborti, Yatinesh Kumari, Ángel Aledo-Serrano, Katina Aleksovska, Marina Koutsodontis Machado Alvim, and Iekhsan Othman. 2018. 'HMGB1: A Common Biomarker and Potential Target for TBI, Neuroinflammation, Epilepsy, and Cognitive Dysfunction', *Frontiers in Neuroscience*, 12.
106. Pegoretti, Valentina, Kathryn A Swanson, John R Bethea, Lesley Probert, Ulrich LM Eisel, and Roman Fischer. 2020. 'Inflammation and oxidative stress in multiple sclerosis: consequences for therapy development', *Oxidative medicine and cellular longevity*, 2020: 7191080.
107. Pepper, Leslie. 2013. *The Green Coffee Bean Quick Weight Loss Diet: Turbo Charge Your Weight Loss and Eat What You Love* (St. Martin's Griffin).
108. Phillips, J Theodore, Michael Hutchinson, Robert Fox, Ralf Gold, and Eva Havrdova. 2014. 'Managing flushing and gastrointestinal events associated with delayed-release dimethyl fumarate: experiences of an international panel', *Multiple sclerosis and related disorders*, 3: 513-19.
109. Ploumi, Christina, Ioanna Daskalaki, and Nektarios Tavernarakis. 2017. 'Mitochondrial biogenesis and clearance: a balancing act', *The FEBS journal*, 284: 183-95.
110. Ponath, Gerald, Matthew R Lincoln, Maya Levine-Ritterman, Calvin Park, Somiah Dahlawi, Mayyan Mubarak, Tomokazu Sumida, Laura Airas, Shun Zhang, and Cigdem Isitan. 2018. 'Enhanced astrocyte responses are driven by a genetic risk allele associated with multiple sclerosis', *Nature communications*, 9: 5337.
111. Popescu, B. F., I. Pirko, and C. F. Lucchinetti. 2013. 'Pathology of multiple sclerosis: where do we stand?', *Continuum (Minneap Minn)*, 19: 901-21.
112. Rafiee Zadeh, A., K. Ghadimi, A. Ataei, M. Askari, N. Sheikhinia, N. Tavoosi, and M. Falahatian. 2019. 'Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2', *Int J Physiol Pathophysiol Pharmacol*, 11: 105-14.
113. Rebai, Olfa, Manel Belkhir, María Victoria Sanchez-Gomez, Carlos Matute, Sami Fattouch, and Mohamed Amri. 2017. 'Differential molecular targets for neuroprotective effect of chlorogenic acid and its related compounds against glutamate induced excitotoxicity and oxidative stress in rat cortical neurons', *Neurochemical research*, 42: 3559-72.
114. Roshan, Hanieh, Omid Nikpayam, Meghdad Sedaghat, and Golbon Sohrab. 2018. 'Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance and appetite in patients with the metabolic syndrome: a randomised clinical trial', *British Journal of Nutrition*, 119: 250-58.
115. Sadeghian, Mona, Vincenzo Mastrolia, Ali Rezaei Haddad, Angelina Mosley, Gizem Mullali, Dimitra Schiza, Marija Sajic, Iain Hargreaves, Simon Heales, and Michael R Duchen. 2016. 'Mitochondrial dysfunction is an important cause of neurological deficits in an

inflammatory model of multiple sclerosis', *Scientific reports*, 6: 33249.

116. Sahni, Sumit, Angelica M Merlot, Sukriti Krishan, Patric J Jansson, and Des R Richardson. 2014. 'Gene of the month: BECN1', *Journal of Clinical Pathology*, 67: 656-60.
117. Satoh, Jun-ichi, Tamako Misawa, Hiroko Tabunoki, and Takashi Yamamura. 2008. 'Molecular network analysis of T-cell transcriptome suggests aberrant regulation of gene expression by NF-κB as a biomarker for relapse of multiple sclerosis', *Dis Markers*, 25: 27-35.
118. Scarisbrick, Isobel A, SI Blaber, CF Lucchinetti, CP Genain, M Blaber, and M Rodriguez. 2002. 'Activity of a newly identified serine protease in CNS demyelination', *Brain*, 125: 1283-96.
119. Scarisbrick, Isobel A, Rachel Linbo, Alexander G Vandell, Mark Keegan, Sachiko I Blaber, Michael Blaber, Diane Sneve, Claudia F Lucchinetti, Moses Rodriguez, and Eleftherios P Diamandis. 2008. 'Kallikreins are associated with secondary progressive multiple sclerosis and promote neurodegeneration'.
120. Scarisbrick, Isobel A, Hyesook Yoon, Michael Panos, Nadya Larson, Sachiko I Blaber, Michael Blaber, and Moses Rodriguez. 2012. 'Kallikrein 6 regulates early CNS demyelination in a viral model of multiple sclerosis', *Brain Pathology*, 22: 709-22.
121. Schauf, Marion, Harini Chinthapatla, Seema Dimri, Edward Li, and Daniel M Hartung. 2023. 'Economic burden of multiple sclerosis in the United States: A systematic literature review', *Journal of Managed Care & Specialty Pharmacy*, 29: 1354-68.
122. Schlossmann, Jens, Robert Feil, and Franz Hofmann. 2003. 'Signaling through NO and cGMP-dependent protein kinases', *Annals of medicine*, 35: 21-27.
123. Shah, Murad-Ali, Ju-Bin Kang, Dong-Ju Park, Myeong-Ok Kim, and Phil-Ok Koh. 2022. 'Chlorogenic acid alleviates cerebral ischemia-induced neuroinflammation via attenuating nuclear factor kappa B activation', *Neuroscience letters*, 773: 136495.
124. Sharifi-Rad, Mehdi, Chintha Lankatillake, Daniel A Dias, Anca Oana Docea, Mohamad Fawzi Mahomoodally, Devina Lobine, Paul L Chazot, Begum Kurt, Tugba Boyunegmez Tumer, and Ana Catarina Moreira. 2020. 'Impact of natural compounds on neurodegenerative disorders: from preclinical to pharmacotherapeutics', *Journal of Clinical Medicine*, 9: 1061.
125. Shen, Wenjuan, Renbin Qi, Jing Zhang, Zhigang Wang, Huadong Wang, Chaofeng Hu, Yanru Zhao, Man Bie, Yanping Wang, and Yongmei Fu. 2012. 'Chlorogenic acid inhibits LPS-induced microglial activation and improves survival of dopaminergic neurons', *Brain Research Bulletin*, 88: 487-94.
126. Shi, Xiaowen, Nian Zhou, Jieyi Cheng, Xunlong Shi, Hai Huang, Mingmei Zhou, and Haiyan Zhu. 2019. 'Chlorogenic acid protects PC12 cells against corticosterone-induced neurotoxicity related to inhibition of autophagy and apoptosis', *BMC Pharmacology and Toxicology*, 20: 1-10.
127. Shusharina, N., D. Yukhnenko, S. Botman, V. Sapunov, V. Savinov, G. Kamyshov, D. Sayapin, and I. Voznyuk. 2023. 'Modern Methods of Diagnostics and Treatment of Neurodegenerative Diseases and Depression', *Diagnostics (Basel)*, 13.
128. Simpson, Steve, Wendy Wang, Peter Otahal, Leigh Blizzard, Ingrid A. F. van der Mei, and Bruce V. Taylor. 2019. 'Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis', *Journal of Neurology, Neurosurgery & Psychiatry*, 90: 1193.
129. Song, Y., W. Wang, B. Wang, and Q. Shi. 2023. 'The Protective Mechanism of TFAM on Mitochondrial DNA and its Role in Neurodegenerative Diseases', *Mol Neurobiol*.
130. Song, Ying, Wenjun Wang, Beibei Wang, and Qiwen Shi. 2023. 'The Protective Mechanism of TFAM on Mitochondrial DNA and its Role in Neurodegenerative Diseases', *Molecular Neurobiology*: 1-10.
131. Stassart, RM, W Mobius, KA Nave, and JM Edgar. 2018. "The axon-myelin unit in development and degenerative disease. Front Neurosci. 2018; 12: 467." In.: Epub 2018/07/28. doi: 10.3389/fnins. 2018.00467. PubMed PMID: 30050403.
132. Subedi, Lalita, Bhakta Prasad Gaire, Sun-Yeou Kim, and Amna Parveen. 2021. 'Nitric oxide as a target for phytochemicals in anti-neuroinflammatory prevention therapy', *Int J Mol Sci*, 22: 4771.
133. Sun, Yan, Huoying Chen, Jiapei Dai, Huijuan Zou, Ming Gao, Hao Wu, Bingxia Ming, Lin Lai, Yifan Xiao, and Ping Xiong. 2015. 'HMGB1 expression patterns during the progression of experimental autoimmune encephalomyelitis', *Journal of neuroimmunology*, 280: 29-35.
134. Tanida, Isei. 2010. 'Autophagosome Formation and Molecular Mechanism of Autophagy', *Antioxid Redox Signal*, 14: 2201-14.
135. Taso, Orjona V, Anastassios Philippou, Athanasios Moustogiannis, Evangelos Zevolis, and Michael Koutsilieris. 2019. 'Lipid peroxidation products and their role in neurodegenerative diseases', *Annals of research hospitals*, 3.

136. Terayama, Ryuji, Yoshio Bando, Ying-Ping Jiang, Branka Mitrovic, and Shigetaka Yoshida. 2005. 'Differential expression of protease M/neurosin in oligodendrocytes and their progenitors in an animal model of multiple sclerosis', *Neuroscience letters*, 382: 82-87.
137. Terayama, Ryuji, Yoshio Bando, Takayuki Takahashi, and Shigetaka Yoshida. 2004. 'Differential expression of neuropsin and protease M/neurosin in oligodendrocytes after injury to the spinal cord', *Glia*, 48: 91-101.
138. Tilokani, L., S. Nagashima, V. Paupe, and J. Prudent. 2018. 'Mitochondrial dynamics: overview of molecular mechanisms', *Essays Biochem*, 62: 341-60.
139. Tofighi, Nahaleh, Masoumeh Asle-Rousta, Mehdi Rahnema, and Rahim Amini. 2021. 'Protective effect of alpha-linoleic acid on Aβ-induced oxidative stress, neuroinflammation, and memory impairment by alteration of α7 nAChR and NMDAR gene expression in the hippocampus of rats', *Neurotoxicology*, 85: 245-53.
140. Tran, S., W. D. Fairlie, and E. F. Lee. 2021. 'BECLIN1: Protein Structure, Function and Regulation', *Cells*, 10.
141. Trapp, Bruce D, and Klaus-Armin Nave. 2008. 'Multiple sclerosis: an immune or neurodegenerative disorder?', *Annu. Rev. Neurosci.*, 31: 247-69.
142. Vallabhapurapu, Sivakumar, and Michael Karin. 2009. 'Regulation and function of NF-κB transcription factors in the immune system', *Annual review of immunology*, 27: 693-733.
143. Walton, Clare, Rachel King, Lindsay Rechtman, Wendy Kaye, Emmanuelle Leray, Ruth Ann Marrie, Neil Robertson, Nicholas La Rocca, Bernard Uitdehaag, Ingrid van der Mei, Mitchell Wallin, Anne Helme, Ceri Angood Napier, Nick Rijke, and Peer Baneke. 2020. 'Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition', *Multiple Sclerosis Journal*, 26: 1816-21.
144. Wang, Di, Liuyang Tian, Huan Lv, Zhihua Pang, Dong Li, Zhuhua Yao, and Shuo Wang. 2020. 'Chlorogenic acid prevents acute myocardial infarction in rats by reducing inflammatory damage and oxidative stress', *Biomedicine & Pharmacotherapy*, 132: 110773.
145. Wang, Hechen, Lu Tian, Yiman Han, Xiaoyao Ma, Yuanyau Hou, and Gang Bai. 2022. 'Mechanism assay of honeysuckle for heat-clearing based on metabolites and metabolomics', *Metabolites*, 12: 121.
146. Wang, Peng-Fei, Fei Jiang, Qiu-Ming Zeng, Wei-Fan Yin, Yue-Zi Hu, Qiao Li, and Zhao-Lan Hu. 2024. 'Mitochondrial and metabolic dysfunction of peripheral immune cells in multiple sclerosis', *Journal of neuroinflammation*, 21: 28.
147. Wang, Yan, Erin Xu, Phillip R Musich, and Fang Lin. 2019. 'Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure', *CNS neuroscience & therapeutics*, 25: 816-24.
148. Watanabe, Masahiko, Yoshiaki Toyama, and Akiko Nishiyama. 2002. 'Differentiation of proliferated NG2-positive glial progenitor cells in a remyelinating lesion', *Journal of neuroscience research*, 69: 826-36.
149. Watts, Michelle E, Roger Pocock, and Charles Claudianos. 2018. 'Brain energy and oxygen metabolism: emerging role in normal function and disease', *Frontiers in molecular neuroscience*, 11: 216.
150. Widder, K., G. Harauz, and D. Hinderberger. 2020. 'Myelin basic protein (MBP) charge variants show different sphingomyelin-mediated interactions with myelin-like lipid monolayers', *Biochim Biophys Acta Biomembr*, 1862: 183077.
151. Wilson, David M, Mark R Cookson, Ludo Van Den Bosch, Henrik Zetterberg, David M Holtzman, and Ilse Dewachter. 2023. 'Hallmarks of neurodegenerative diseases', *Cell*, 186: 693-714.
152. Wirawan, Ellen, Saskia Lippens, Tom Vanden Berghe, Alessandra Romagnoli, Gian Maria Fimia, Mauro Piacentini, and Peter Vandenabeele. 2012. 'Beclin1: a role in membrane dynamics and beyond', *Autophagy*, 8: 6-17.
153. Witte, M. E., D. J. Mahad, H. Lassmann, and J. van Horssen. 2014. 'Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis', *Trends Mol Med*, 20: 179-87.
154. Wittkowski, H, D Viemann, A Lueken, K Barczyk, T Vogl, J Roth, and D Foell. 2008. 'The Damage Associated Molecular Pattern (DAMP) molecule S100A12 induces pro-inflammatory responses in monocytes via innate immunity signalling pathways', *Pediatric Rheumatology*, 6: 1-1.
155. Wootla, Bharath, Makoto Eriguchi, and Moses Rodriguez. 2012. 'Is Multiple Sclerosis an Autoimmune Disease?', *Autoimmune Diseases*, 2012: 969657.
156. Xiong, S., X. Su, Y. Kang, J. Si, L. Wang, X. Li, and K. Ma. 2023. 'Effect and mechanism of chlorogenic acid on cognitive dysfunction in mice by lipopolysaccharide-induced neuroinflammation', *Front Immunol*, 14: 1178188.
157. Xu, Zhu, Feng Zhang, FangLi Sun, KeFeng Gu, Shuai Dong, and Dian He. 2015. 'Dimethyl fumarate for multiple sclerosis', *Cochrane Database of Systematic Reviews*.
158. Yan, Hua, Yan-Qiong Gao, Ying Zhang, Huan Wang, Gui-Sheng Liu, and Jian-Yuan Lei. 2018. 'Chlorogenic acid alleviates autophagy and insulin resistance by suppressing JNK pathway in a rat model of nonalcoholic fatty liver disease', *Journal of biosciences*, 43: 287-94.
159. Yan, Jun, Clay M Winterford, Vibeke S Catts, Betty K Pat, Michael P Pender, Pamela A McCombe, and Judith

M Greer. 2018. 'Increased constitutive activation of NF-κB p65 (RelA) in peripheral blood cells of patients with progressive multiple sclerosis', *Journal of neuroimmunology*, 320: 111-16.

160. Yoon, Hyesook, and Isobel A. Scarisbrick. 2016. 'Kallikrein-related peptidase 6 exacerbates disease in an autoimmune model of multiple sclerosis', *Biological chemistry*, 397: 1277-86.
161. Yu, Lei-Min, Li-Qi Mao, Chun-Yan Wu, Wei Ye, and Xi Wang. 2021. 'Chlorogenic acid improves intestinal barrier function by downregulating CD14 to inhibit the NF-κB signaling pathway', *Journal of Functional Foods*, 85: 104640.
162. Zha, Zheng, Sisi Liu, Yijiang Liu, Chen Li, and Lei Wang. 2022. 'Potential Utility of Natural Products against Oxidative Stress in Animal Models of Multiple Sclerosis', *Antioxidants*, 11: 1495.
163. Zhang, Qian, Michael J Lenardo, and David Baltimore. 2017. '30 years of NF-κB: a blossoming of relevance to human pathobiology', *Cell*, 168: 37-57.
164. Zhao, Yuan, Chaoran Wang, Tianyuan Yang, Guofeng Feng, Haoyang Tan, Xue Piao, Dongni Chen, Yu Zhang, Wenjign Jiao, and Yongping Chen. 2023. 'Chlorogenic acid alleviates chronic stress-induced intestinal damage by inhibiting the P38MAPK/NF-κB pathway', *Journal of Agricultural and Food Chemistry*, 71: 9381-90.
165. Zheng, Yihui, Luyao Li, Binwen Chen, Yu Fang, Wei Lin, Tianlei Zhang, Xiaoli Feng, Xiaoyue Tao, Yiqing Wu, and Xiaoqin Fu. 2022. 'Chlorogenic acid exerts neuroprotective effect against hypoxia-ischemia brain injury in neonatal rats by activating Sirt1 to regulate the Nrf2-NF-κB signaling pathway', *Cell Communication and Signaling*, 20: 84.
166. Zhou, Yifan, Chunping Cui, Xiaoyu Ma, Wenjing Luo, Song Guo Zheng, and Wei Qiu. 2020. 'Nuclear factor κB (NF-κB)–mediated inflammation in multiple sclerosis', *Frontiers in Immunology*, 11: 391.
167. Ziemssen, Tjalf, Josef Hoffman, Rainer Apfel, and Simone Kern. 2008. 'Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis', *Health and quality of life outcomes*, 6: 1-6