

Protective roles of resveratrol in multiple sclerosis treatment: a review of preclinical studies



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ABSTRACT

Multiple sclerosis (MS) is a complex disorder characterized by inflammation and neurodegeneration within the central nervous system (CNS). Resveratrol (RES) is a naturally occurring polyphenolic compound with broad antioxidant and anti-inflammatory properties. As the most common demyelinating disease of the CNS, MS is defined by perivascular inflammation, demyelination, and axonal loss. This review aims to systematically evaluate the preclinical evidence for RES in MS models, elucidate its molecular mechanisms, and identify gaps that limit clinical translation. Preclinical investigations consistently demonstrate the beneficial impact of RES in animal models of MS through its remyelinating, anti-inflammatory, and antioxidant activities, as well as its protective effects on the blood-brain barrier. RES, in addition to the aforementioned effects, has also been shown in pre-clinical studies to improve MS through mechanisms such as Sirtuin 1 (SIRT1) activation, T-cell apoptosis, modulation of the miR-124/sphingosine kinase 1 axis, and enhancement of autophagy. Although RES exhibits several promising therapeutic properties, confirmation through robust clinical trials is essential before recommending RES as a treatment option for patients with MS.

Keywords:

Multiple sclerosis
Demyelination
Resveratrol
Oxidative stress
Neuroprotection

Introduction

Multiple sclerosis (MS) is a chronic immunemediated, inflammatory, and neurodegenerative disorder of the central nervous system (CNS) that leads to a wide range of irreversible clinical disabilities (Margoni et al., 2022). MS is more prevalent among young and middleaged adults, with a female:male ratio of approximately 3:1 (Barati et al., 2020). Histopathological features of MS include large focal demyelinating lesions in both gray

matter (cerebral and cerebellar cortex, basal ganglia, brainstem, and spinal cord) and white matter, followed by axonal injury and neurodegeneration (Mojaverrostami et al., 2022). The extent of axonal degeneration resulting from myelin loss varies among patients and even among lesions within the same individual (Haider et al., 2014; Lassmann 2018). The National MS Society classifies MS into four major clinical categories based on disease progression: (1) primary progressive MS (PPMS),

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characterized by continuous neurological decline without remission; (2) secondary progressive MS (SPMS), marked by progressive neurological deterioration following an initial relapsing-remitting course, (3) relapsing-remitting MS (RRMS), the most common subtype (approximately 80%) (Priyadarshi Prajjwal 2023) defined by acute episodes of neurological dysfunction (relapses) followed by periods of clinical stability (remission); and (4) progressive-relapsing MS (PRMS), affecting about 5% of cases and associated with progressive worsening accompanied by acute relapses (Barati et al., 2020; Rivera and Aigner 2012). Etiological factors such as genetic susceptibility, environmental triggers like Epstein-Barr virus infection, vitamin D deficiency, or smoking, interact with immune dysregulation, aberrant T-cell and B-cell activation, and microglial-mediated neuroinflammation to ultimately drive central nervous system autoimmunity and the development of MS (Javanbakht et al., 2023a; Lassmann et al., 2007). Various effector cells participate in this process, including autoreactive T cells such as Th1 and Th17 subsets, CD8⁺ cytotoxic T cells, B lymphocytes, and plasma cells (Lassmann et al., 2007; Van Langelaar et al., 2020). Recent evidence suggests that microglial activation, reactive oxygen species (ROS) overproduction, and mitochondrial dysfunction are key mechanisms driving neurodegeneration in MS. Given the central role of oxidative stress in these pathways, the use of antioxidants may help counteract these processes and potentially slow disease progression (Cotsapas et al., 2018). While reducing relapse frequency and slowing disease progression remain central therapeutic goals in MS, a comprehensive treatment strategy must also address symptom management, improve quality of life, and promote neurorepair and remyelination, all of which are essential for optimizing long-term patient outcomes.

Recent studies have provided compelling evidence that long-term adherence to a diet rich in plant-derived polyphenols may offer protection against a variety of diseases, including cancers, diabetes, cardiovascular disorders, osteoporosis, and neurodegenerative conditions (Arts and Hollman 2005; Javanbakht et al., 2023a; Javanbakht et al., 2023b). RES exhibits a broad spectrum of biological activities, which can be organized into primary effects most relevant to MS, such as antioxidant, anti-inflammatory, and immunomodulatory actions, and secondary systemic effects, including

cardioprotective, hypolipidemic, anticancer, anti-aging, and hypotensive properties (Dasgupta and Milbrandt 2007; Tomé-Carneiro et al., 2013b; Zhou et al., 2021). Although both cis- and trans-isomers of RES exist in nature, with the trans form being more abundant and biologically active, its poor oral bioavailability, driven by rapid hepatic metabolism and limited BBB penetration, substantially constrains its therapeutic translation to CNS disorders such as MS (Flores et al., 2016). RES is showing benefits in major neurodegenerative diseases such as Parkinson's disease, Amyotrophic Lateral Sclerosis, MS, and Huntington's disease. It enhances mitochondrial performance by activating the AMPK/SIRT1/PGC1 α pathway, thereby improving oxidative capacity and ATP production. Evidence indicates that RES modulates key mechanisms of neurodegeneration, including oxidative stress, inflammatory signaling, mitochondrial dysfunction, and neuronal survival (Haoyu Wang 2026; Kasra Shahsavari 2026).

This review aims to elucidate the beneficial effects of RES in MS by synthesizing findings from recent pre-clinical studies. Given the current lack of robust clinical evidence, our findings may help guide future clinical research.

Specifically, we highlight the molecular neuroprotective mechanisms of RES and discuss its potential therapeutic relevance for patients with MS. In the following sections, we first summarize the etiological factors and immunopathology of MS, then review the biological properties and mechanisms of action of RES, and finally evaluate the preclinical evidence regarding its effects in MS.

Finally, we discuss clinical implications, limitations of current research, and future directions.

Chemical and Pharmacokinetic Properties of Resveratrol

Polyphenols are phenylpropanoids synthesized by plants as secondary metabolites in response to unfavorable conditions, such as exposure to pathogens or adverse weather. More than 8000 phenolic molecules have been discovered, which contain at least one aromatic ring and one or more -OH groups. They are categorized as flavonoids (flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanins) with a C6-C3-C6 structure, and non-flavonoid molecules (phenolic acids, hydroxycinnamic acids, Stilbenes, Lignans, and Tan-

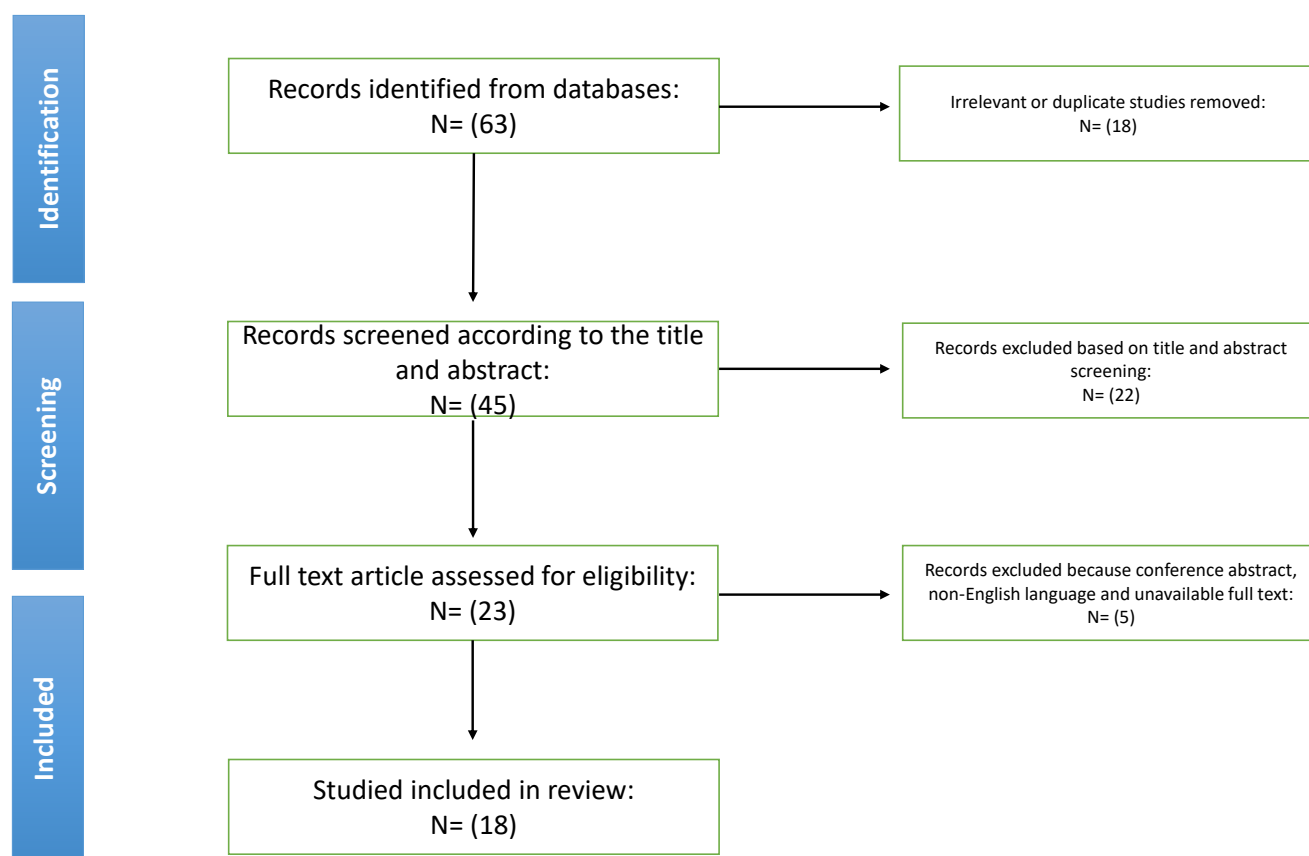


FIGURE 1. Flow chart of the literature search and selection of articles.

nins) (Di Lorenzo et al., 2021). RES; 3,4',5trihydroxystilbene, also known as 3,4',5stilbenetriol is a natural stilbenetype polyphenol biosynthesized by many plants in response to adverse conditions such as mechanical injury, environmental stress, pathogenic attack (including fungal and bacterial infections), and ultraviolet (UV) exposure (Jeandet et al., 2010). To date, RES has been identified in numerous dietary sources, including grapes, peanuts, blueberries, bilberries, cranberries, rhubarb, mulberries, soybeans, pomegranates, and purple grape juice (Fonseca-Santos and Chorilli 2020; Tian and Liu 2020). Several nonedible plants, such as specific grasses, lilies, and pine bark, also produce RES (Zhang et al., 2021a). RES has a molecular weight of 228.247 g/mol and a melting point of 253–255°C (Griñán-Ferré et al., 2021; Zhang et al., 2021b). Structurally, it consists of two aromatic rings connected by a double styrene bond and exists in two isomeric forms—cis and trans—capable of interconversion due to the presence of a C=C double bond (Luca et al., 2020; Tian and Liu 2020). Most of the documented biological and therapeutic effects of

RES are attributed to the trans isomer, which is considered the more stable and biologically active form (Fabjanowicz et al., 2018) (Figure 1).

In the intestines, RES can either undergo passive diffusion or interact with membrane transporters. Upon absorption, RES undergoes rapid and extensive metabolism, leading to a short initial half-life of the primary molecule (Giancchetti and Fierabracci 2020). After oral ingestion, RES reaches its peak plasma concentration within 30 to 90 minutes (Zhang et al., 2021b). RES has a low oral bioavailability of less than 1% due to its rapid metabolism in the liver and intestines. Approximately 20 different metabolites of RES have been detected in the plasma, urine, and tissues of both animals and humans. These metabolites are primarily produced through three pathways: glucuronidation and sulfation in the liver and intestines, and transformation by gut microbes (Gambini et al., 2015; Tomé-Carneiro et al., 2013a). The results of in vitro studies demonstrate that RES can easily cross the BBB due to its lipid solubility and molecular weight (228 Da) (Amri et al., 2012;

Griñán-Ferré et al., 2021). The limited solubility of RES in water (<0.05 mg/ml) presents a considerable obstacle in creating a formulation with optimal bioavailability for this compound (Colica et al., 2018).

Materials and Methods

In this narrative review, a comprehensive literature search was conducted to identify relevant publications on RES effects in MS. To identify relevant studies, two independent reviewers conducted a comprehensive literature search in Scopus, Google Scholar, Web of Science and PubMed/MEDLINE from inception to 1 January 2026 using the following title/abstract (ti/ab) keywords: “Multiple sclerosis” [MeSH Terms], OR “Demyelination model” [MeSH Terms], OR “Experimental autoimmune encephalomyelitis” [MeSH Terms], OR “Cuprizone demyelination model” [MeSH Terms], AND “Resveratrol” [MeSH Terms], OR “Resveratrol derivatives” [MeSH Terms]. Reference lists of all selected articles and their bibliographies were screened to identify additional studies. Furthermore, the bibliographies of the included publications were examined to ensure that no pertinent research was overlooked. All of the studies that matched our keywords, including in vitro/in vivo animal models and human clinical trials, were reviewed. Original articles and case reports were included, while review articles, conference abstracts, and non-English articles were excluded.

Pathophysiological Mechanisms of MS Disease

MS is a chronic inflammatory disease of the CNS that affects both white and gray matters, generally occurs as a result of two main pathophysiological processes: focal neuroinflammation leading to macroscopic inflammatory plaques in the white matter of the brain and spinal cord, and damage to the blood-brain barrier (BBB) (La Rosa et al., 2023a; Lee et al., 2012). The consequences of this process manifest as demyelination, gliosis, axonal damage, and neuronal loss (Frohman et al., 2006). In general, neuroaxonal damage is observed in primary and chronic demyelinated lesions, which correlate with patient disability, while acute-stage lesions are associated with a high infiltration of immune cells (Gh Popescu and Lucchinetti 2012; Witte et al., 2009). By altering the permeability of the BBB, peripheral immune cells (CD4⁺ and CD8⁺ T lymphocytes) and macrophages infiltrate the CNS and form demyelinated plaques, leading

to the degradation of the myelin sheath and oligodendrocytes (Dendrou et al., 2015; Schepici et al., 2019).

Based on the in vivo and in vitro studies, it is suggested that MS is a T cell-mediated autoimmune disease (Haase and Linker 2021). Lymphocytes have a crucial role in the development and regulation of immune responses through the secretion of cytokines. Specifically, Th1 lymphocytes activate macrophages and stimulate the production of reactive oxygen and nitrogen species (ROS and RNS) by producing interferons (IFN). Additionally, the production of IL-12 by Th1 lymphocytes enhances the generation of IFN (Schepici et al., 2019). Moreover, Th1 cells express high levels of the $\alpha 4 \beta 1$ integrin VLA-4, which facilitates their influx to the CNS through interaction with VCAM-1 (Haase and Linker 2021). On the other hand, Th17 lymphocytes contribute to the development of inflammation by releasing cytokines such as IL-17, IL-21, and IL-22 (Schepici et al., 2019). IL-17 can potentially disrupt the BBB by generating ROS. Moreover, in patients with MS, the high expression of IL-17 receptors in the endothelial cells enables their transmigration into the CNS, independent of BBB disruption. The overproduction of Th17 cells and IL-17 can interfere with the regulation of tight junctions in the brain, which can facilitate the entry of Th17 cells into the CNS at the cellular level (Moser et al., 2020).

Oxidative stress, defined by excessive production of ROS and RNS, is a major contributor to neuronal and axonal injury in MS and is implicated in disease pathology across all stages (Adamczyk and Adamczyk-Sowa 2016). The accumulation of oxidized lipids, nucleotides, and proteins provides strong evidence for ROS/RNS involvement in MS. In active and progressive MS lesions, damaged oligodendrocytes and degenerating axons display markedly increased levels of oxidized lipids and nucleotides (Haider et al., 2011; Plemel et al., 2015). Furthermore, the activity of nitric oxide synthase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, key enzymes responsible for generating nitric oxide and superoxide, has been shown to be significantly elevated in MS lesions (Fischer et al., 2012). Moreover, activated microglia and macrophages in MS not only generate oxidative bursts but also produce reactive aldehydes that persist for 1-2 minutes. These aldehydes can spread and cause damage in distant areas after a delay. This feature has an important implication for the pathogenesis and progression of MS (Fischer et

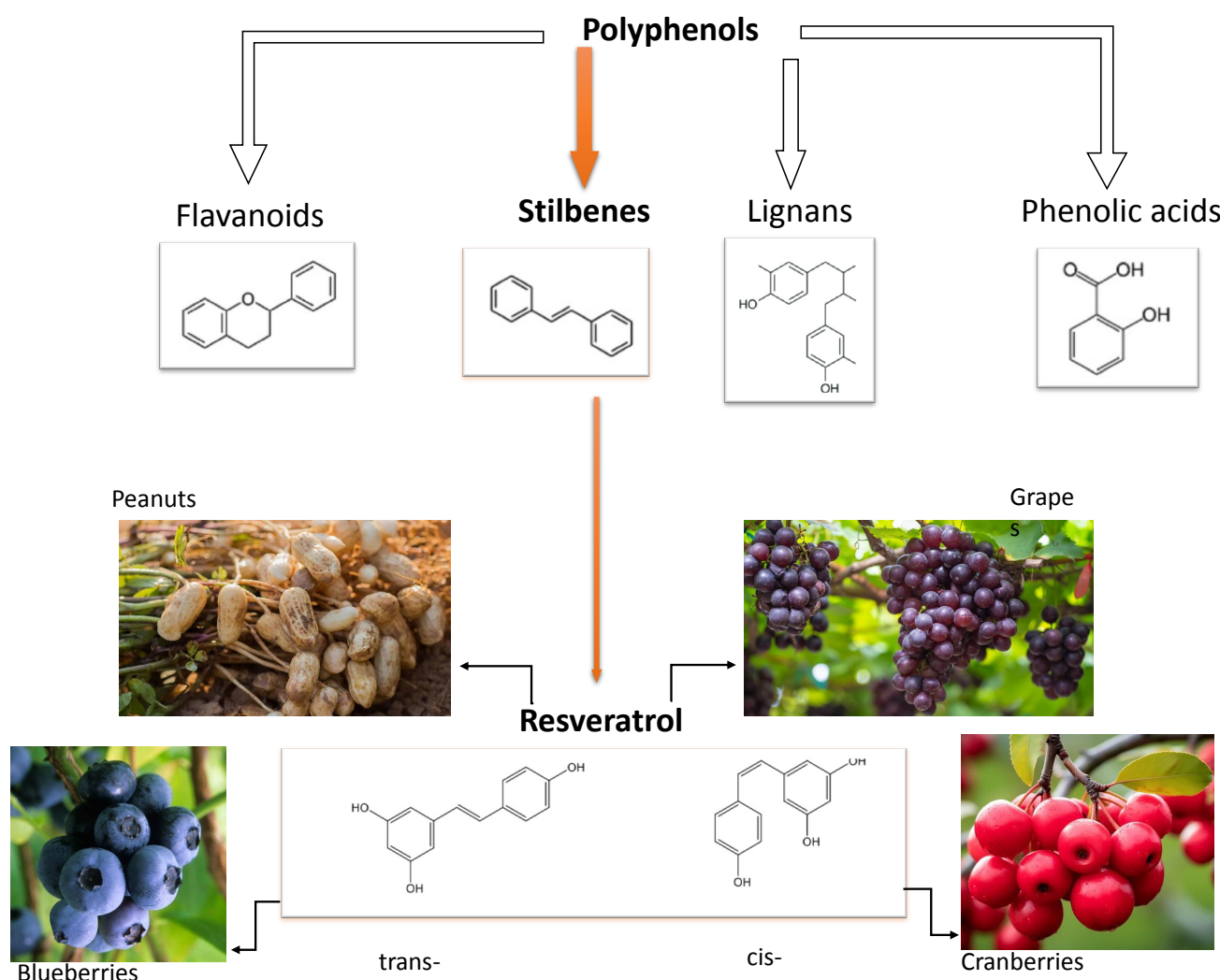


FIGURE 2. Polyphenol classes, the configurations of Resveratrol (trans- cis), and its sources.

al., 2012). The activation of the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway effectively prevents the development of MS by regulating specific enzyme levels. Studies have indicated that the JNK and ERK signaling pathways can activate Nrf2. Nrf2 activates the Nrf2-ARE (erythroid-derived 2-like 2) antioxidant-responsive element. This pathway is vital for protecting cells from oxidative stress and may be a potential target for activating antioxidant mechanisms in MS (Javanbakht et al., 2023c).

Mechanisms Underlying the Anti-Multiple Sclerosis Effects of Resveratrol

Numerous studies have investigated the neuroprotective potential of RES in various neurodegenerative

disorders, including Alzheimer's disease (AD) (Arbo et al., 2020; Kong et al., 2019; Kwon et al., 2010; Lin et al., 2018; Regitz et al., 2016; Sun et al., 2019; Zhao et al., 2018), Parkinson's disease (PD) (Arbo et al., 2020; Gaballah et al., 2016; Kung et al., 2021; Liu et al., 2019; Palle and Neerati 2018), Huntington's disease (HD) (La Rosa et al., 2023b; Tellone et al., 2015), and Amyotrophic lateral sclerosis (ALS) (Mancuso et al., 2014; Novak et al., 2021; Yun et al., 2019) by examining its effects on behavior, neurochemical pathways, and cerebral blood flow (Figure 2) (Table 1).

Strengthening the BBB integrity

As previously described, the progression of MS is closely associated with disruption of the BBB, which

TABLE 1: Resveratrol effects on preclinical and clinical models of MS.

Author and year	Type of Study	Model of MS	Doses and administration routes	Treatment period	Outcomes
Keramatzadeh et al., 2025	Double-blind, randomized placebo-controlled trial	55 Relapsing-remitting MS patients	Patients were instructed to take 2 capsules of 250 mg of resveratrol daily	8 weeks	RES treatment significantly decreased TNF- α , and MDA compared to the placebo, while TG and fatigue scale remained unchanged.
Villar-Delfino et al., 2024	In vitro	Granulocytes and peripheral blood mononuclear cells (PBMCs) Relapsing-remitting MS, Primary progressive MS	Res (10 μ M) among the wells of 96-well flat-bottomed culture plates	72 h	RES inhibited inflammation-associated ROS production in unstimulated and stimulated granulocytes from patients with MS and healthy controls. RSV did not affect cytokine secretion in cells from patients with MS; however, this antioxidant decreased IL-6 levels in mononuclear cells from the control group.
Shamsher et al., 2024	In vivo	EAE in C57/B16 mice	8.44 mg/kg, RES nanoparticles, intranasal administration	30 days	RES nanoparticles administered intranasally in EAE mice diminished the retinal ganglion cell (RGC) loss in optic neuritis. RES nanoparticles administered intranasally indicated stronger neuroprotective effects on RGC compared to the oral administration with same RES nanoformulation.
El-Sayed et al., 2024	In vivo	Cuprizone-intoxicated rats	Iron oxide nanoparticles loaded with RES, oral dose of 0.5 ml of iron oxide nanoparticles -RES (10 mg/kg)	2 weeks	Iron oxide nanoparticles loaded with RES showed stronger neuroprotective effects compared to the free RES via decreasing demyelination and neuroinflammation through downregulation of TNF- α and S100 β expression.
Shamsher et al., 2023	In vivo	EAE in C57/B16 mice	16.9 mg/kg RES nanoparticles, oral administration / 8.44 mg/kg, RES nanoparticles, intranasal administration	1 month	Neither oral nor intranasal administrations reduced spinal cord or optic nerve inflammation or demyelination. But the protective effects for RGC cells were same particularly oral administration indicated additional neuroprotective effects via reducing paralysis.
Zheng et al., 2023	In vivo	EAE in C57/B16 mice	Daily doses of RES-loaded exosomes derived from macrophages (3 mg/kg RSV, 30 μ L), intranasal administration	16 days	Exosomes derived from macrophages loaded with RES significantly improved EAE disease severity via improving myelin recovery of MS lesions and decreasing inflammatory responses in the CNS (TGF- β , IFN- γ , IL-1 β , IL-6, IL-17 and IL-10).
Shamsher et al., 2023	In vivo	EAE in C57/B16 mice	16.9 mg/kg RES nanoparticles, oral administration	1 month	RES nanoparticles treatment did not reduce inflammation and demyelination in the spinal cord and the optic nerve, while were able to decrease RGC loss compared to the vehicle.
Samy et al., 2023	In vivo	Cuprizone-intoxicated C57Bl/6 mice	250 mg/kg/day- daily, oral administration	For 5 weeks starting from the third week.	Improving motor deficits, suppressing apoptosis, alleviating demyelination, and enhancing remyelination through the activation of autophagic pathways, which may involve SIRT1/FOXO1 pathway activation
Tecellioglu 2022,	In vivo	C57BL/6J female mice	20 mg/kg daily for seven days, oral administration	Seven days	RES treatment prevented EAE-induced oxidative stress in brain tissue by decreasing lipid peroxidation and enhancing antioxidant defense systems. Furthermore, RES reversed the histopathological changes in caspase-3 and IL-17 activity, as well as the elevated cytokine levels (TNF- α and IL-1 β) in brain tissue.

Continuation of Table 1:

Author and year	Type of Study	Model of MS	Doses and administration routes	Treatment period	Outcomes
Gandy et al.,2019	In vivo	EAE in C57/Bl6 mice	100 mg/kg of RES- daily, oral administration	Beginning on day 2 following immunization to day 15 post-immunization	RES treatment decreased EAE severity, including neuroinflammation and immune cell infiltration in CNS via alteration of the miR-124/SK1 axis
Ghaiaid et al., 2017	In vivo	Cuprizone-intoxicated C57Bl/6 mice	250 mg/kg/day of RES- daily, oral administration	For 3 weeks starting from the second week	Improving motor coordination and balance, increasing remyelination by increasing Olig expression and promote OPC differentiation, enhancing mitochondrial function, reducing oxidative stress, and inhibiting NF-kB signaling
Wang et al.,2016	In vivo	EAE in C57/Bl6 mice	10, 25, and 50 mg/kg of RES- once a day by i.p. injection	For 20 consecutive days s started on the day of immunization	Maintaining the BBB integrity
Wang et al., 2016	In vivo	EAE in C57/Bl6 mice	30 mg/kg of RES, once a day by i.p. injection	For consecutive 7 days after EAE induction	A significant decrease in IFN- γ and TNF- α Th1 cytokines, and an increase in IL-4 and IL-10 Th2 cytokines. A significant reduction in clinical scores.
Sato et al., 2013	In vivo	EAE in C57/BL6 mice and TMEV-IDD in SJL/J mice	A diet containing 0.04% RES provided approximately 20 mg/kg per day- by chowing	EAE: during the induction (days 1 to 8; Early) or effector (days 14 to 23; Late) phase, or through the whole course (days 1 to 63; Whole) of EAE. TMEV-IDD: during the chronic phase (days 35 to 48; Chronic) of TMEV infection.	Exacerbation of demyelination and inflammation without neuroprotection in the CNS in both models
Fonseca-Kelly et al., 2012	In vivo	Chronic EAE in C57/Bl6 mice	100 and 250 mg/kg of RES- once daily oral gavage	30 days	Delaying the onset of EAE. Neuroprotective effects by preventing neuronal loss without immunosuppression. An Increase in the Number of Retinal Ganglion Cells (RGCs) in the Optic Nerve Inflammation of EAE Mice
Shindler et al., 2010	In vivo	EAE in SJL/J mice	500 or 1000 mg/kg SRT501(a pharmaceutical-grade formulation of RES)- Daily, oral administration	Beginning on day 8 post-immunization and repeated daily until sacrifice on day 14.	Neuroprotective effects on RGCs by reducing neuronal damage in optic nerves and spinal cords in EAE through a mechanism involving SIRT1 activation

Continuation of Table 1:

Author and year	Type of Study	Model of MS	Doses and administration routes	Treatment period	Outcomes
Imler et al., 2009	In vivo	EAE in SJL/J mice	AIN93G diets supplemented with 0.02%, 0.04%, or 0.08% RES.	Starting at EAE immunization	Induction of apoptosis in active T cells leads to a decrease in serum levels of cytokines IFN- γ and IL-12, as well as chemokines MIP1A, MCP-1, RANTES, and Eotaxin. Conversely, there is an increase in serum levels of IL-17 and G-CSF. Decreased expression of IL-6 by macrophages
			0.04% RES provided approximately 22 mg/kg/day by chowing		
Singh et al., 2007	In vivo	EAE in C57/BL6 mice	100 mg/kg of RES-daily by oral gavage	From day 2 until the termination of experiment	Decreasing inflammatory responses by down-regulation of TNF- α , IFN- γ , interleukin (IL)-2, IL-9, IL-12, IL-17, MIP-1 α MCP-1, RANTES, and Eotaxin.
	In Vitro	T cells from wild-type (C57BL/6)	5–50 μ M	–	Induction of high levels of apoptosis in activated T cells, and to a lesser extent in inactive T cells, through the activation of aryl AhR and ER

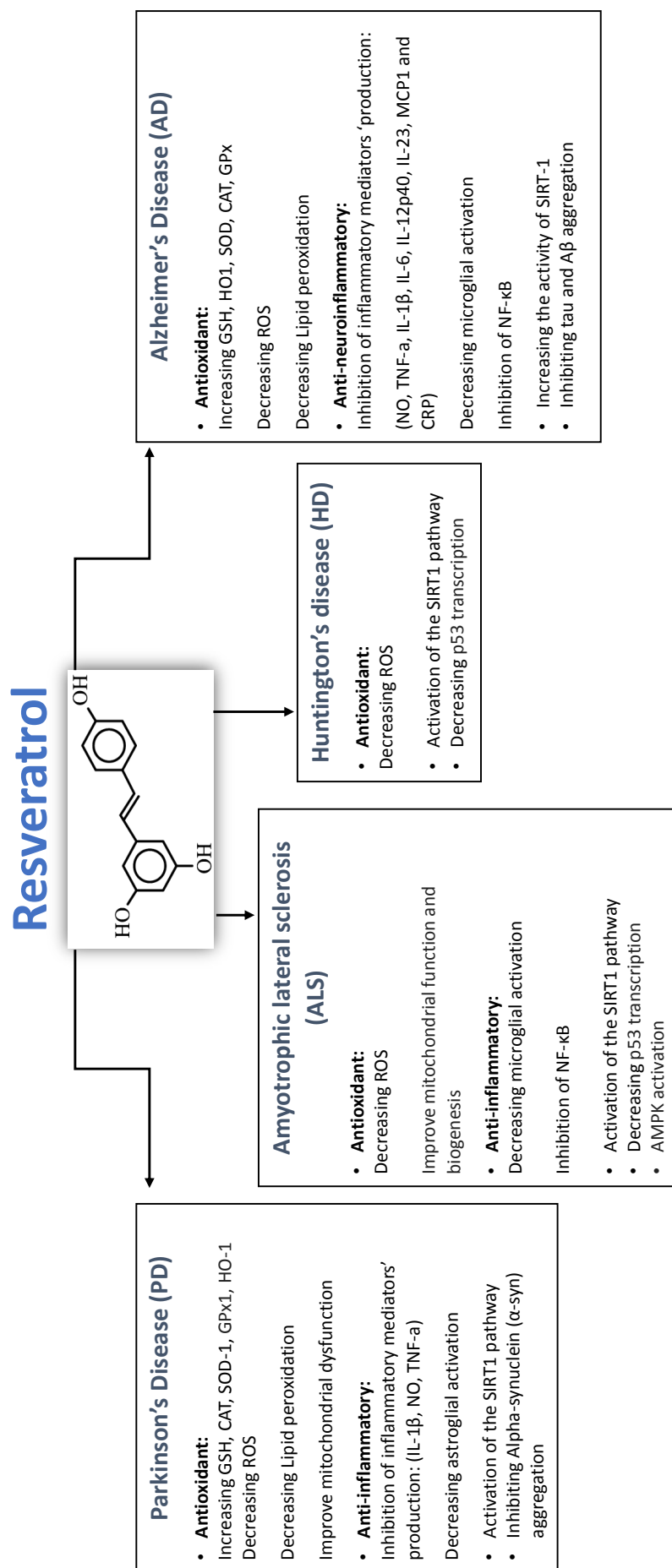


FIGURE 3. Neuroprotective mechanism of Resveratrol in Neurodegenerative diseases

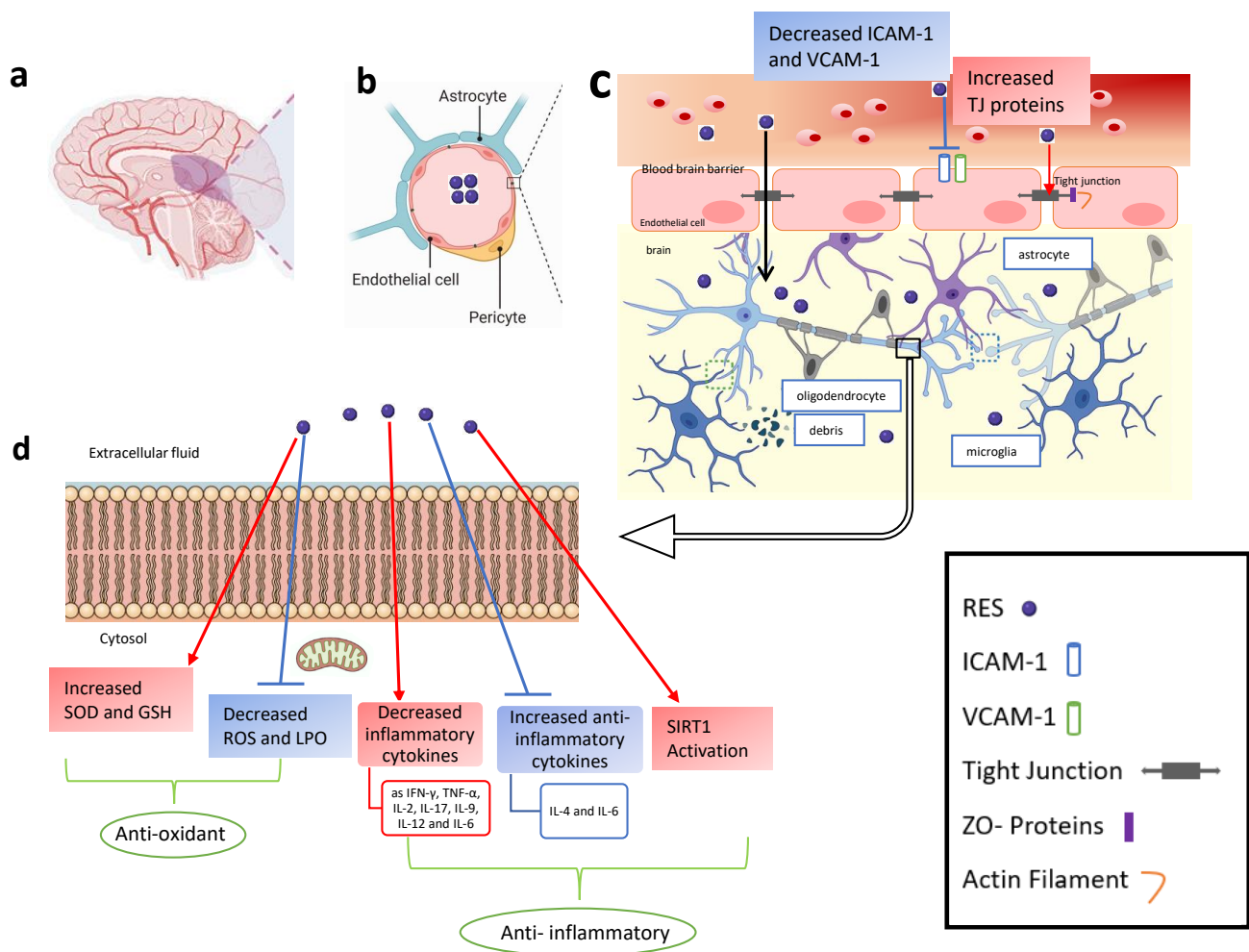


FIGURE 4. Neuroprotective effects of Resveratrol in MS. a) brain, b) BBB structure, c) role of RES in reinforcement of BBB integrity by increasing TJ proteins (ZO-1, occludin, and claudin-5) and decreasing the expression of adhesion molecules (VCAM-1 and ICAM-1). d) antioxidative and anti-inflammatory roles of RES in MS Lesions.

permits the entry of pro-inflammatory immune cells and toxic molecules into the CNS. This breach contributes to cerebral edema, demyelination, and ultimately neuronal cell death (Wang et al., 2016b). The structural integrity of the BBB is primarily maintained by tight junction (TJ) proteins, also known as zonula occludens. The degradation or disassembly of these TJ proteins is believed to underlie cytokine-induced BBB breakdown in experimental autoimmune encephalomyelitis (EAE), the most widely used animal model of MS (Yang et al., 2016).

It is well established that the organization and expression of TJ proteins undergo significant alterations during the progression of MS and EAE (Bennett et al., 2010). ZO-1, the principal cytoplasmic scaffolding protein associated with TJs, plays a critical role in linking the C-terminal domains of occludin and claudins to the

underlying actin cytoskeleton. Reductions in the expression of ZO-1 or occludin markedly increase BBB permeability (Zhang et al., 2013). Pro-inflammatory cytokines exert particularly detrimental effects on ZO-1 and occludin compared with other TJ components (Förster 2008). Preclinical studies in EAE mice have demonstrated that resveratrol (RES; 25 and 50 mg/kg) significantly upregulates the transmembrane TJ proteins ZO-1, occludin, and claudin-5 in a dose-dependent manner during the chronic phase of the disease. Furthermore, RES treatment reduces the overexpression of adhesion molecules ICAM-1 and VCAM-1 in EAE mice. This restoration of BBB integrity is associated with an improvement in clinical symptoms, including reductions in tail and hind-limb paralysis (Wang et al., 2016b).

Alongside BBB disruption, interactions between ad-

hesion molecules expressed on leukocytes and endothelial cells of the BBB play a pivotal role in facilitating immune-cell infiltration into the CNS during both EAE and MS (Chaudhary et al., 2006). Vascular cell adhesion molecule-1 (VCAM-1) mediates the attachment of pathogenic CD4⁺ T cells to endothelial cells, whereas intercellular adhesion molecule-1 (ICAM-1) supports T-cell retention on the endothelial surface and promotes their migration across the BBB via diapedesis. Diffuse upregulation and heightened activity of ICAM-1 and VCAM-1 on endothelial cells, astrocytes, and microglia within active MS and EAE lesions have long been recognized as key contributors to disease progression (Yang et al., 2016a). RES treatment has been shown to suppress the overexpression of ICAM-1 and VCAM-1 in the brain tissue of EAE mice (Wang et al., 2016b).

RES strengthens BBB integrity by downregulating adhesion and binding proteins, thereby limiting the entry of immune cells into the CNS. Additionally, RES reduces the expression of adhesion molecules and chemokines, impairing the adhesion and transendothelial migration of inflammatory cells from the abluminal to the luminal side of the BBB. Consequently, in EAE, RES exhibits potent anti-inflammatory and immunosuppressive effects by reducing the infiltration of activated immune cells that drive neuroinflammation and myelin damage.

Although the reviewed studies collectively suggest that RES may exert protective effects on BBB integrity and immune-cell trafficking in EAE, several limitations temper the strength of these conclusions. Much of the evidence derives from single-model, short-duration murine experiments that may not fully capture the heterogeneity or chronicity of MS pathology, raising concerns about translational relevance. The reported upregulation of TJ proteins such as ZO-1, occludin, and claudin-5 following RES administration is compelling, yet these findings rely heavily on semi-quantitative assays and lack complementary functional measurements of barrier permeability, making it difficult to determine whether molecular changes translate into physiologically meaningful improvements. Similarly, reductions in ICAM-1 and VCAM-1 expression are frequently interpreted as evidence of attenuated leukocyte infiltration, but few studies directly quantify immune-cell trafficking or distinguish between effects on endothelial cells versus glial populations. Moreover, the dose-dependent benefits observed in EAE models contrast with reports of exac-

erbated inflammation in other MS-related paradigms, suggesting that RES effects may be context-dependent and influenced by formulation, bioavailability, or disease stage. Taken together, while the available data indicate that RES can modulate BBB-related pathways, the evidence base remains constrained by methodological variability and limited mechanistic depth, underscoring the need for more rigorous, multimodal studies before firm therapeutic claims can be made.

Attenuation of Oxidative Stress

Lipids constitute approximately 70% of the dry weight of myelin, and lipid peroxidation is a critical driver of MS progression. Clinical studies have linked MS exacerbations to elevated levels of lipid peroxidation products (LPOs) in the cerebrospinal fluid (CSF). LPOs possess neurotoxic and pro-inflammatory properties, providing a mechanistic link between oxidative stress and the processes of demyelination and axonal injury in MS (Frid et al., 2015; Ghaiaid et al., 2017). In the cuprizone model of demyelination, mice exhibit a marked increase in lipid peroxidation (LPOs) accompanied by a significant reduction in glutathione (GSH) levels. Additionally, the activities of superoxide dismutase (SOD) in both mitochondrial and post-mitochondrial fractions are diminished, resulting in suppression of the brain's antioxidant enzyme system (Praet et al., 2014). In an in vitro study, the effects of RES were investigated on ROS production and cytokine release using luminol-dependent chemiluminescence and ELISA. The results showed that RES significantly downregulated ROS production in both resting and stimulated granulocytes from MS patients and healthy controls. Regarding cytokine levels, RES reduced IL-6 by 49% in the control group but had no effect on IL-6 levels in the MS group. Interestingly, higher levels of IL-10 were detected in MS patient supernatants compared to controls, while no significant changes were observed in IL-1 β or HMGB1 levels. The findings suggest that RES can effectively modulate ROS production in MS, highlighting its potential as a promising adjunct therapy for controlling oxidative innate immune responses in inflammatory diseases (Villar-Delfino et al., 2024).

RES exerts potent neuroprotective effects by shielding neurons from oxidative injury, reducing lipid peroxidation, and enhancing key components of the endogenous antioxidant defense system (Tecelioğlu et

al., 2022). Owing to its strong free-radical-scavenging capacity, RES decreases LPO levels, elevates GSH content, and restores both mitochondrial and post-mitochondrial SOD activity in the cuprizone mouse model of MS (Ghaiad et al., 2017). The antioxidant properties of polyphenolic compounds, including RES, are largely attributed to the redox activity of their phenolic hydroxyl groups and their ability to delocalize electrons across their aromatic structure (Rossi et al., 2013). In the only clinical study conducted to date evaluating the effects of RES in patients with MS, it was observed that daily 500 mg of RES oral intake for 8 weeks decreased TNF- α and MDA compared to the placebo group, while TG and fatigue scale remained unchanged in RRMS patients (Keramatzadeh et al., 2025).

Despite substantial evidence implicating lipid peroxidation as a major driver of demyelination and axonal injury in MS, the studies evaluating RES's antioxidant effects remain constrained by several methodological and translational limitations. Much of the supporting data derives from the cuprizone model, which while useful for studying oligodendrocyte toxicity does not recapitulate the full immunopathological complexity of MS, limiting the generalizability of findings such as restored GSH levels and SOD activity. The *in vitro* study demonstrating RES-mediated suppression of ROS production in granulocytes provides mechanistic insight, yet its mixed cytokine results, particularly the absence of IL-6 reduction in MS patients, underscore the variability of RES responsiveness across immune contexts. Moreover, the sole clinical trial to date, although suggestive of reduced TNF- α and MDA levels after short-term supplementation, is limited by its small sample size, brief duration, and lack of functional or imaging endpoints, making it difficult to determine whether biochemical improvements translate into meaningful clinical benefit. The heavy reliance on oxidative-stress biomarkers, without parallel assessment of demyelination, axonal preservation, or long-term neuroprotection, further restricts interpretation.

Attenuation of Neuroinflammation

RES has the ability to decrease inflammatory cytokines such as IFN- γ , TNF- α , IL-2, IL-17, IL-9, IL-12, and IL-6, while boosting the levels of anti-inflammatory cytokines like IL-4 and IL-10. This shift in the equilibrium between pro-inflammatory and anti-inflammatory

cytokines, resulting in a Th1:Th2 ratio of less than 1, triggers improved immunomodulatory effects in the brains of EAE mice (Singh et al., 2007; Tecellioglu et al., 2022; Wang et al., 2016a).

RES can reduce inflammatory cytokines through various mechanisms: 1) suppressing the activity of enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), 2) by exerting inhibitory effects on transcription factors like nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1), which regulate the expression of inflammatory mediators (de la Lastra and Villegas 2005). In one EAE model of MS, RES treatment just postponed the onset of EAE by a few days. Also they found that RES prevented the loss of retinal ganglion cells and delay both neurological paralysis and visual function (Fonseca-Kelly et al., 2012).

Interestingly, in contrast to the majority of studies reporting neuroprotective effects of RES, one investigation examining two MS models, EAE and Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), found that dietary RES not only failed to confer neuroprotection but actually exacerbated demyelination and CNS inflammation (Sato et al., 2013). Although the precise mechanisms underlying this unexpected outcome were not identified, the authors suggested that poor oral bioavailability and limited CNS permeability of RES may have contributed to the lack of therapeutic efficacy. Animal studies suggest that resveratrol's vasodilatory effects may inadvertently facilitate leukocyte adhesion and transmigration by increasing vessel diameter and altering blood-flow dynamics. In our models, this was reflected by greater meningitis and perivascular cuffing, indicating enhanced inflammatory cell infiltration into the CNS. Because immune cell entry is a key driver of MS pathology, and therapies such as natalizumab improve outcomes by blocking this migration—these findings imply that resveratrol-induced vasodilation may worsen neuroinflammation under experimental conditions. Recent advances in drug-delivery technologies, particularly the use of exosome-based systems, have generated considerable interest due to their unique biological advantages. In a recent EAE study, RES encapsulated within macrophage-derived exosomes markedly improved disease severity, significantly reduced CNS inflammatory responses (TGF- β , IFN- γ , IL-1 β , IL-6, IL-17, and IL-10), and dramatically decreased the expression of Iba-1⁺ microglia and NF- κ B

in the CNS of EAE mice (Zheng et al., 2023). These findings highlight the potential of exosome-mediated delivery to overcome the pharmacokinetic limitations of RES and enhance its therapeutic efficacy in MS. In an EAE model of MS in C57BL/6J female mice. In the treatment groups received oral RES at 20 mg/kg daily for seven days. The results demonstrated that RES treatment prevented EAE-induced oxidative stress in brain tissue by decreasing lipid peroxidation and enhancing antioxidant defense systems. Furthermore, RES reversed the histopathological changes in caspase-3 and IL-17 activity, as well as the elevated cytokine levels (TNF- α and IL-1 β) in brain tissue. Elevated TNF- α and IL-1 β levels in blood serum were also reduced, and neurological deficits were reversed in RES-treated EAE mice (Tecellioğlu et al., 2022). These findings suggest that RES effectively prevents oxidative, immunological, and histological changes in the brain caused by EAE, and these beneficial effects are likely due to its strong antioxidant and anti-inflammatory properties.

Although numerous preclinical studies suggest that RES exerts broad immunomodulatory effects in EAE by suppressing pro-inflammatory cytokines, enhancing Th2-associated mediators, and inhibiting key inflammatory pathways such as iNOS, COX-2, NF- κ B, and AP-1, the overall evidence remains heterogeneous and context-dependent. Much of the evidence supporting the reported benefits, including delayed disease onset, reduced retinal ganglion cell loss, and attenuation of oxidative and cytokine-driven injury, come from short-term, single-strain murine models that may not fully capture the complexity of MS immunopathology. The contradictory findings from Sato et al., where dietary RES exacerbated demyelination and inflammation in both EAE and TMEV-IDD, underscore the importance of pharmacokinetics, formulation, and route of administration; poor oral bioavailability and limited CNS penetration likely contributed to the lack of efficacy, while RES-induced vasodilation may have inadvertently facilitated leukocyte infiltration, worsening neuroinflammation. These discrepancies highlight a critical gap between molecular mechanisms and in vivo outcomes, as many studies infer therapeutic benefit from cytokine shifts without directly quantifying immune-cell trafficking, demyelination, or axonal preservation. Emerging delivery strategies, such as macrophage-derived exosome encapsulation, show promise in overcoming these

limitations by enhancing CNS targeting and amplifying anti-inflammatory effects, yet these findings remain preliminary and confined to early-stage animal work.

Apoptosis of Activated T cells

As previously noted, both CD4⁺ T cells, particularly Th1 and Th17 subsets, and CD11b⁺ myeloid cells, including macrophages and microglia, contribute to the complex immune responses that drive inflammation, demyelination, and neurodegeneration in MS. Treatment with RES reduces the proportions of these immune-cell populations in the brains of EAE mice and diminishes T-cell activation as well as the expression of immune-stimulatory molecules. These reductions are thought to result from G0/G1 cell-cycle arrest and apoptosis (Gandy et al., 2019). RES, similar to other polyphenolic compounds, can directly and indirectly modulate the activity of the aryl hydrocarbon receptor (AhR). AhR modulation suppresses downstream transcriptional programs and can induce apoptosis (Singh et al., 2011). In EAE mice, RES induces apoptosis in activated T cells through AhR and estrogen receptor (ER) signaling, accompanied by upregulation of AhR, Fas, and FasL expression (Singh et al., 2007).

Emerging evidence suggests that miR-124 plays an important role in regulating immune responses and neuroinflammation in MS. Dysregulation of miR-124 in immune cells, including T cells and microglia, may contribute to myelin damage and neurodegeneration observed in MS patients (Abolghasemi et al., 2023). RES appears to enhance miR-124 expression in mononuclear cells infiltrating the CNS by modulating AhR activity. Furthermore, RES inhibits sphingosine kinase-1 (SK1), thereby altering the miR-124/SK1 regulatory axis in encephalitogenic CD4⁺ T cells in EAE. This modulation halts cell proliferation, induces apoptosis, and ultimately reduces EAE severity (Gandy et al., 2019). Although the available studies suggest that RES can attenuate neuroinflammation in EAE by reducing pathogenic CD4⁺ T-cell subsets, suppressing CD11b⁺ myeloid activation, and inducing apoptosis through G0/G1 arrest, these findings remain constrained by several mechanistic and translational uncertainties. Much of the evidence relies on ex vivo analyses of immune-cell proportions and apoptosis markers, without parallel assessment of functional outcomes such as antigen-specific T-cell responses, microglial phenotypic switching, or long-term

effects on demyelination and axonal integrity. The proposed involvement of AhR and ER signaling in RES-induced T-cell apoptosis is intriguing but largely inferred from correlative upregulation of AhR, Fas, and FasL, with limited causal validation or exploration of cell-type specificity. Similarly, while modulation of the miR-124/SK1 axis offers a compelling link between RES and the regulation of encephalitogenic T-cell proliferation, these findings stem from a narrow set of experimental conditions and do not address whether similar regulatory dynamics occur in chronic or relapsing disease stages. The broader relevance of miR-124 dysregulation in human MS also remains insufficiently defined, as most supporting data derive from small cohorts or animal models.

SIRT1 Activation

RES, one of the most potent natural sirtuin-activating compounds (STACs), enhances both the expression and enzymatic activity of SIRT1, a mammalian NAD-dependent deacetylase. Binding of RES to the N-terminal domain of SIRT1 can increase its catalytic activity up to twofold, although this effect is typically observed at higher RES concentrations (Albani et al., 2010).

Growing evidence indicates that the biological actions of resveratrol cannot be fully attributed to SIRT1 activation, suggesting that a substantial portion of its effects are SIRT1 independent (Park et al., 2012). Although resveratrol was initially characterized as a potent STAC, subsequent studies demonstrated that it also modulates multiple signaling pathways—including AMPK, PI3K/Akt, NFκB, and mitochondrial biogenesis, independently of SIRT1, and that some phenotypes persist even in SIRT1 deficient models (Price et al., 2012). This has contributed to the ongoing STAC controversy, centered on whether resveratrol and related polyphenols activate SIRT1 directly or indirectly. Early *in vitro* assays suggested direct allosteric activation of SIRT1, but later analyses revealed that these effects were highly dependent on fluorophoretagged substrates, raising concerns about assay artifacts (Borra et al., 2005). Studies support a model in which resveratrol enhances SIRT1 activity indirectly, primarily through AMPK activation, increased NAD⁺ availability, or modulation of upstream metabolic sensors (Lin et al., 2018; Tian et al., 2016). Collectively, these findings indicate that resveratrol's pharmacology is multifaceted, and that its interaction with SIRT1 represents only one component of a broader, more complex

mechanism of action.

The deacetylase activity of SIRT1 regulates transcription by modifying specific protein substrates, particularly histones. Histone acetylation promotes gene transcription by loosening chromatin structure and increasing DNA accessibility to transcriptional machinery. Conversely, SIRT1-mediated deacetylation removes acetyl groups from histones, resulting in chromatin condensation and transcriptional repression (Imler and Petro 2009). Through this mechanism, SIRT1 plays a central role in modulating gene expression and cellular responses.

Importantly, activation of SIRT1 alone is insufficient to suppress inflammation when treatment is initiated after disease onset. However, SIRT1 activators may potentiate the effects of existing immunomodulatory therapies and act synergistically with them to improve clinical outcomes (Shindler et al., 2010).

Activation of SIRT1 by RES promotes histone deacetylation, leading to reduced transcription of inflammatory cytokines such as IL-6. In addition, RES-mediated SIRT1 activation decreases the expression of multiple inflammatory mediators by deacetylating the NF-κB RelA/p65 subunit, a key transcription factor regulating cytokines including IL-6 and IL-23 (Imler and Petro 2009; Yeung et al., 2004). Pharmaceutical-grade SRT501, a specialized formulation of RES, has demonstrated significant neuroprotective effects as a SIRT1 activator in EAE mice. SRT501 reduces neuronal dysfunction during recovery, protects against axonal injury, and prevents neuronal loss. These findings suggest that SIRT1 activators such as RES may represent a promising therapeutic strategy to prevent long-term visual impairment associated with optic neuritis and to limit permanent neurological deficits in MS models (Shindler et al., 2010).

Overexpression of SIRT1 in transgenic EAE mice exerts both immunomodulatory and neuroprotective effects. These benefits arise from reduced levels of pro-inflammatory cytokines such as IL-17 and IFN-γ, alongside increased production of the anti-inflammatory cytokine IL-10. SIRT1 overexpression also decreases the activation of caspase-3, a key effector of apoptosis (La Rosa et al., 2023b). SIRT1 promotes a shift toward a regulatory monocyte phenotype and enhances anti-inflammatory pathways, thereby fostering a neuroprotective environment. In EAE, the anti-inflammatory actions

of SIRT1 are closely associated with the induction of brain-derived neurotrophic factor (BDNF). BDNF protects against demyelination and axonal injury, supports neuronal survival, and contributes to tissue repair and regeneration in MS.

Mechanistically, SIRT1 is thought to deacetylate and activate Transcription Co-activator 1 (TORC1) by facilitating its dephosphorylation. Activated TORC1 interacts with CREB (cAMP response element-binding protein), a key transcription factor that drives BDNF expression through the TORC1/CREB signaling axis (Nimmagadda et al., 2013).

Collectively, while SIRT1-related mechanisms provide a compelling framework for understanding some of RES's neuroprotective and anti-inflammatory effects, the current evidence base is fragmented and heavily model-dependent, highlighting the need for more rigorous, mechanistically integrated studies to clarify the true contribution of SIRT1 to RES-mediated benefits in MS.

Remyelination-enhancing ability

The cuprizone model of MS leads to a marked reduction in myelin-associated proteins, including myelin basic protein (MBP), which stabilizes myelin structure through lipid interactions, and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), an enzyme essential for oligodendrocyte maturation and myelin integrity (Fulton et al., 2009; Nave 2010). In mice with cuprizone-induced demyelination, oral administration of RES significantly increased MBP and CNP levels. These improvements are attributed to enhanced antioxidant capacity, reduced inflammation, and improved mitochondrial function.

RES also counteracted the cuprizone-induced reduction in Olig-1 expression, a transcription factor that promotes the differentiation of oligodendrocyte progenitor cells (OPCs) and supports remyelination. Collectively, these findings indicate that RES may enhance remyelination in demyelinating conditions (Dai et al., 2015; Ghaiad et al., 2017).

The NF- κ B signaling pathway in oligodendrocytes involves a heterodimer composed of p50 and p65 (Rel-A). Upon activation, NF- κ B induces rapid phosphorylation of I κ B- α , rendering phosphorylated I κ B- α (pI κ B- α) susceptible to proteasomal degradation (Mc Guire et al., 2013). RES inhibits NF- κ B activation in oligodendrocytes of cuprizone-intoxicated mice by suppressing Rel-A upregulation and reducing pI κ B- α levels. This

inhibition promotes OPC differentiation and facilitates remyelination. Behavioral improvements, including enhanced balance and motor coordination, further support the remyelinating effects of RES in this model (Ghaiad et al., 2017).

Growing evidence indicates that autophagy plays a crucial role in CNS remyelination by promoting the maturation and differentiation of OPCs into myelinating oligodendrocytes (Bankston et al., 2019; Smith et al., 2013). RES activates autophagy and reverses cuprizone-induced suppression of autophagic flux, as demonstrated by an increased LC3-II/LC3-I ratio and reduced SQSTM1/p62 expression. RES treatment also enhances the formation of autophagosomes and autolysosomes, indicating restoration of functional autophagy (Samy et al., 2023). SIRT1 further contributes to autophagy regulation by promoting the deacetylation, activation, and nuclear translocation of FoxO1, which subsequently upregulates several autophagy-related genes. As a result, expression of Rab7, a small GTPase essential for autophagosome lysosome fusion, is increased, supporting efficient autophagic degradation (Wang et al., 2014).

Recent findings indicate that cuprizone toxicity suppresses SIRT1 and FoxO1 expression in the corpus callosum, whereas RES effectively reverses this suppression by promoting SIRT1- and FoxO1-mediated deacetylation. This restoration of SIRT1/FoxO1 activity enhances autophagic flux and facilitates efficient autophagic degradation, ultimately contributing to improved remyelination in cuprizone-intoxicated mice (Samy et al., 2023).

Recent advances in nanotechnology have enabled innovative drug-delivery strategies that markedly improve bioavailability, solubility, and the ability of therapeutic agents to cross the BBB (Kumari et al., 2022). Nanoformulations of polyphenols represent a promising approach to enhance the therapeutic potential of these natural compounds, particularly in neurodegenerative disorders (Kumari et al., 2022; Liu et al., 2023). Several recent studies have evaluated nanoformulated RES in MS animal models. Shamsher et al. conducted a series of investigations assessing the effects of RES nanoparticles administered intranasally or orally in EAE mice (Shamsher et al., 2024a; Shamsher et al., 2024b; Shamsher et al., 2023). One month of oral RES-nanoparticle treatment reduced disease severity and retinal ganglion cell (RGC) loss; however, it did not attenuate inflamma-

tion or demyelination in the spinal cord or optic nerve (Shamsher et al., 2023).

In a separate study, intranasal administration of RES nanoparticles for one month enhanced RGC survival at half the oral dose, demonstrating superior delivery efficiency (Shamsher et al., 2024b). When comparing the two routes, both intranasal and oral administration provided comparable neuroprotection against RGC loss, but oral delivery offered additional benefits by reducing paralysis. Notably, neither route produced meaningful reductions in demyelination or inflammation (Shamsher et al., 2024a). El-Sayed et al. further reported that iron-oxide nanoparticles loaded with RES exhibited stronger anti-inflammatory effects via downregulation of TNF- α and S100 β and greater remyelination potential in the cuprizone model compared with free RES (El-Sayed et al., 2024).

Although multiple studies suggest that RES enhances remyelination in the cuprizone model by restoring MBP, CNP, and Olig-1 expression, these findings remain limited by the inherent constraints of this toxin-induced demyelination paradigm, which lacks the adaptive immune component central to MS pathology. The reported improvements in oligodendrocyte differentiation and behavioral outcomes are compelling, yet most studies rely on short-term biochemical markers without integrating ultrastructural or long-term functional assessments to confirm true remyelination. Similarly, the proposed inhibition of NF- κ B signaling in oligodendrocytes is supported primarily by reductions in Rel-A and pI κ B- α expression, but causal evidence linking these molecular changes to restored myelin architecture is sparse. The emerging role of autophagy in OPC maturation adds mechanistic depth, however studies demonstrating RES-mediated restoration of autophagic flux via LC3-II/LC3-I ratios, p62 degradation, and SIRT1/FoxO1-dependent Rab7 upregulation are limited to single-model analyses and do not address whether these pathways operate similarly in inflammatory or chronic demyelinating contexts. Nanoformulation studies further complicate interpretation: while RES nanoparticles improve retinal ganglion cell survival and modestly reduce paralysis, they consistently fail to attenuate demyelination or CNS inflammation, suggesting that enhanced delivery alone may be insufficient to overcome fundamental pharmacodynamic limitations.

Limitation

To date, no large-scale randomized controlled trials have specifically evaluated the therapeutic efficacy of RES in patients with MS, and the available evidence is derived primarily from preclinical studies using experimental models of MS. Beyond the well-recognized pharmacokinetic limitations, including rapid metabolism, low bioavailability, and poor aqueous solubility, several additional translational challenges further restrict the clinical applicability of RES. These include heterogeneity among animal models (e.g., EAE versus cuprizone), the short duration of most preclinical interventions, the absence of standardized dosing regimens across studies, and the lack of long-term safety and toxicity data. Although nanotechnology-based delivery systems such as solid lipid nanoparticles (SLNs), protein-based nanocomplexes, solid dispersions, nanocrystals, and nanostructured lipid carriers (NLCs) have been developed to enhance RES solubility, stability, and bioavailability, these strategies also require systematic evaluation in well-designed in-vivo and clinical studies to determine their long-term efficacy and safety (Chimento et al., 2019; Meng et al., 2021).

Conclusion

MS is the most prevalent autoimmune disorder of the CNS, and more effective disease-modifying strategies are urgently needed. RES has drawn interest for its proposed neuroprotective and anti-inflammatory effects, yet most supporting evidence comes from preclinical studies, leaving a substantial translational gap. In experimental MS models, RES has been shown to reduce oxidative stress, support remyelination, limit demyelination, strengthen BBB integrity, and modulate inflammatory pathways, indicating potential engagement with multiple mechanisms relevant to MS pathology. However, the evidence remains heterogeneous, and contradictory findings such as those reported by Sato et al., where RES worsened demyelination and inflammation in EAE and TMEV-IDD models, underscore the need for cautious interpretation. Given these inconsistencies, RES should be considered an experimental candidate rather than a validated therapeutic option. Future research should prioritize standardized RES formulations with improved bioavailability, particularly nanoformulations; long-term dosing studies in chronic EAE models; and incorporation of biomarkers of oxidative stress

and neuroinflammation in clinical trials. Additional efforts, including head-to-head comparisons of formulations, combination studies with standard MS therapies, exploration of gut microbiome interactions, and translational work using humanized models or patient-derived cells, may help clarify its therapeutic potential. Overall, while RES interacts with several pathways relevant to MS, its clinical applicability remains uncertain, and rigorous, well-controlled studies are required to determine its true value.

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Conflict of interest

The authors declare no potential conflict of interest.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

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