Common Pathophysiological Molecular Mechanisms Shared Between the Pathogenesis of Obesity and Multiple Sclerosis and the Effects of Various Antioxidant Compounds as Complementary Therapy for Multiple Sclerosis: A Comprehensive Review

Fani-Niki Varra , Olga Pagonopoulou , Michail Varras [*] , Viktoria-Konstantina Varra ,
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Review

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Fani-Niki Varra [1,2]**, Olga Pagonopoulou** [3]**, Michail Varras** [4,*]**, Viktoria-Konstantina Varra** [5] **and Panagiotis Theodosis-Nobelos** [1]

[1] Department of Pharmacy, School of Health Sciences, Frederick University, Nicosia 1036, Cyprus

[2] Medical School, Democritus University of Thrace, 6810 Alexandroupolis, Greece

[3] Laboratory of Physiology, Department of Medicine, Democritus University of Thrace, Alexandroupoli 68100, Greece

[4] Fourth Department of Obstetrics and Gynecology, 'Elena Venizelou' General and Maternity Hospital, Athens 11521, Greece

[5] Department of Pharmacy, School of Health Sciences, University of Patras, Patra 26504, Greece

* Correspondence: mnvarras@otenet.gr

Abstract

Multiple sclerosis (MS), an autoimmune chronic inflammatory disorder of the Central Nervous System (CNS), leading to demyelination of CNS neurons, with its pathology being related with various genetic and environmental factors, such as diet and obesity. Obesity has reached the dimensions of a global epidemic. It is due to excessive fat accumulation and hypertrophy of adipocytes and results in insufficient energy expenditure in combination with genetic, social and environmental factors. The aim of this review is to analyze at molecular level, the relationship of obesity, as a chronic inflammatory condition, with the pathophysiology of MS as a chronic autoimmune inflammatory disease. Particular emphasis is placed on the role of cytokines, adiponectin and oxidative stress (OS) in neuronal damage and the pathogenesis of MS, in order to understand the complex links between obesity and MS. Chronic inflammation and OS, which are implicated and promoted in obesity, are interconnected processes, causing a toxic state, which contributes to the development of CNS neuroinflammation and neuronal damage, resulting in neuronal demyelination and the onset of MS. Adipose tissue is a complex endocrine organ, in addition to being a lipid storage organ, that secretes cytokines and adipokines, which are involved in the regulation of hormones, metabolism, inflammation, and whole-body homeostasis. Obesity triggers a chronic low-grade inflammation causing insulin resistance (IR) and leptin resistance, disruption of the blood-brain barrier (BBB) and brain metabolism, infiltration of the CNS by immune cells, production of reactive oxygen species (ROS), and generation of oxidative stress (OS). Therefore, obesity affects MS through common underlying mechanisms and thus seems to be a modifiable risk factor for this disease, whilst compounds with multi-functional characteristics, and antioxidant and anti-inflammatory potential could be an additive tool towards the progression of MS and its promotion through obesity.

Keywords: obesity; multiple sclerosis; oxidative stress; inflammation; cytokines; adipokines; antioxidants; natural antioxidants

1. Introduction

Obesity is defined as the excessive accumulation of body fat with detrimental effects on human health [1]. It represents a state of chronic, low-grade inflammation that has been associated with a wide range of pathological conditions, such as metabolic syndrome (MetS) and insulin resistance (IR), as well as numerous diseases including type 2 diabetes mellitus (T2DM), increased blood pressure, cardiovascular diseases (CVDs), non-alcoholic fatty liver disease (NAFLD), kidney disorders, musculoskeletal disorders, infertility, psychological problems, specific types of cancer, and autoimmune diseases [2–7]. Dietary shifts observed in recent year, characterized by increased consumption of foods high in fats and sugars, have contributed significantly to the global obesity epidemic [4,8]. According to the World Health Organization (WHO), an estimated 35% of the global population is either overweight [Body Mass Index (BMI), 25–30 kg/m²] or obese (BMI > 30 kg/m²) [9].

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory disease of the central nervous system (CNS), involving demyelination, the destruction of the myelin sheath surrounding nerve fibers and neurodegeneration, whilst these processes impair or block the conduction of nerve impulses along axons [10]. The clinical forms of MS include: (a) relapsing-remitting MS, (b) secondary progressive MS, and (c) primary progressive MS [11]. The disease primarily affects young adults, typically manifesting between the ages of 20 and 50, with a mean age of onset around 30 years [12]. However, MS can also develop in childhood or later in life, beyond the age of 60 [10]. Over the past decades, the global prevalence of MS has been rising, particularly among women [13–16].

MS is thought to arise from the complex interplay of genetic, environmental, and lifestyle factors, including diet and obesity [17–19]. Overweight and obese individuals are reported to have a significantly elevated risk of developing MS [20]. In women diagnosed with MS, obesity at the time of diagnosis has been associated with a relapsing disease course [21]. Moreover, in individuals with MS, a positive correlation has been observed between obesity and disability severity, as measured by higher scores on the Expanded Disability Status Scale (EDSS) [22]. Additionally, comorbid conditions such as T2DM, hypertension, hypercholesterolemia, and peripheral vascular disease appear to be independent risk factors for increased disability in MS patients [21]. There is also evidence linking obesity during childhood, adolescence, and early adulthood with an increased risk of MS development [19,23]. Furthermore, obesity may influence disease progression and response to treatment [10]. Notably, a correlation has been reported between the extent of disability and oxidative stress (OS) in MS patients [22].

The aim of the present study is to investigate at molecular level the potential pathophysiological link between obesity, as a chronic inflammatory condition, and the pathogenesis of MS, which is likewise a chronic inflammatory autoimmune disease of the CNS. This includes the analysis of mechanisms such as the secretion of pro-inflammatory adipokines and cytokines, inflammasome activation, gut microbiota alterations, and oxidative stress. Additionally, the study focuses on the complementary role of multi-functional antioxidant and anti-inflammatory compounds in the treatment of MS, particularly through the resolution of chronic inflammation and oxidative stress.

2. Pathophysiological Association Between Obesity and Multiple Sclerosis

2.1. The Role of Chronic Inflammation in the Pathophysiology of MS

Obesity and multiple sclerosis (MS) share common pathophysiological mechanisms that interconnect them, particularly through the promotion of chronic inflammation, alterations in adipokine and cytokine secretion, associations with oxidative stress, and dysregulation of both the inflammasome and the gut microbiota [24,25].

Obesity is a metabolic condition characterized by adipocyte hypertrophy (increase in cell size) and hyperplasia (increase in cell number) [7,26]. This expansion of adipose tissue promotes the secretion of various chemotactic factors into the bloodstream, such as monocyte chemoattractant proteins MCP-1, -2, -3, and -4; CXCL10 (interferon-gamma-inducible protein 10); eotaxin; and CCL5/RANTES (regulated upon activation, normal T-cell expressed and secreted), all of them

facilitating the recruitment of circulating immune cells [7] (Figure 1). These monocytes are subsequently activated into M1 pro-inflammatory macrophages, replacing the M2 anti-inflammatory phenotype typically found in individuals with normal body weight [7]. M1 macrophages in adipose tissue secrete elevated levels of (a) pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, and (b) pro-inflammatory adipokines including leptin, visfatin, resistin, and plasminogen activator inhibitor-1 (PAI-1). In obesity, the secretion of anti-inflammatory adipokines such as adiponectin and apelin, as well as anti-inflammatory cytokines like IL-10, is reduced [7]. Collectively, these inflammatory changes in adipose tissue contribute to the development of chronic, systemic, low-grade inflammation, which underlies metabolic syndrome (MetS), insulin resistance (IR), type 2 diabetes mellitus (T2DM), and other obesity-related conditions, including MS [7,27]. Obesity also promotes the recruitment and expansion of pro-inflammatory T helper 1 (Th1) and Th17 cells, as well as CD8+ neutrophilic T lymphocytes [28], while reducing anti-inflammatory Th2 and regulatory T (Treg) cells, which are essential for maintaining immune homeostasis [29]. Furthermore, there is a decrease in invariant natural killer T (iNKT) cells and type 2 innate lymphoid cells (ILC2), along with diminished expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), a key regulator of adipose tissue homeostasis [30]. Chronic inflammation in adipose tissue leads to an altered adipokine profile marked by increased secretion of leptin, visfatin, resistin, and PAI-1, and decreased adiponectin, an adipokine with anti-inflammatory properties [7,27].
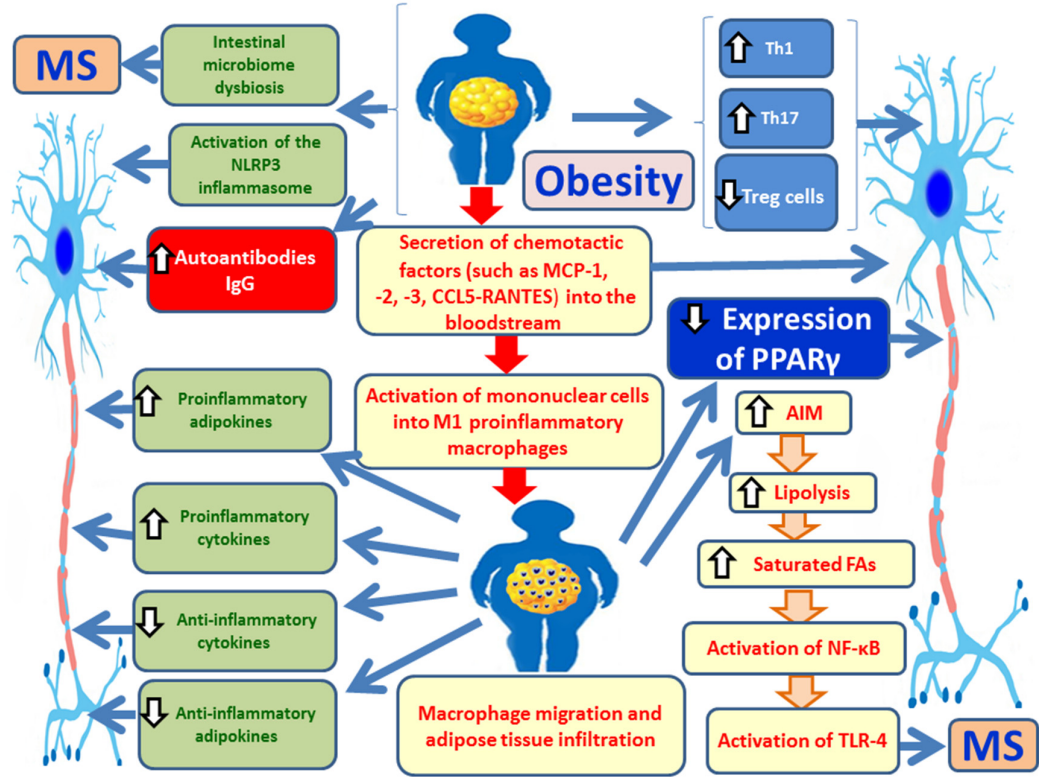

Figure 1. Schematic representation of the main mechanisms by which chronic inflammation contributes to the pathogenesis of multiple sclerosis in obesity. MCP-1: monocyte chemoattractant protein-1; CCL5-RANTES: C-C motif chemokine ligand 5 – regulated upon activation, normal T-cell expressed and secreted; Th1: T helper 1 cells; Th17: T helper 17 cells; Treg: regulatory T lymphocytes; PPAR-γ: peroxisome proliferator-activated receptor gamma; FAs: fatty acids; AIM: apoptosis inhibitor of macrophages; TLR-4: toll-like receptor 4; NF-κB: nuclear factor kappa B.

Similarly, early stages of MS are characterized by chronic inflammation within the CNS, which progresses to neurodegeneration in the later phases of the disease [31]. Chemokines such as MCP-1, -2, -3, and CCL5/RANTES play a critical role in MS pathophysiology [32,33]. The immune profile of

MS mirrors that of obesity, with an increase in Th1 and Th17 cells and a corresponding decrease in Th2 and Treg lymphocytes [28]. The dominance of Th17 cells is particularly implicated in promoting autoimmune inflammation within the CNS, thereby contributing to MS pathogenesis [16]. Additionally, elevated levels of pro-inflammatory adipokines may exacerbate disease progression in obese MS patients [29]. The dysregulated secretion of pro-inflammatory cytokines by adipocytes and macrophages in obesity is also believed to contribute to MS development [16]. Moreover, excessive lipolysis in obesity, driven by macrophage apoptosis inhibitor (AIM) in an attempt to counteract disease progression, results in the release of large amounts of saturated fatty acids (SFAs) [16]. These SFAs activate toll-like receptor 4 (TLR-4), triggering CNS demyelination and inflammation through nuclear factor-kappa B (NF-κB) signaling, thus promoting MS pathogenesis [16,34]. Finally, obesity is associated with increased production of IgG autoantibodies, which are involved in the pathogenesis of several autoimmune diseases, including MS [16].

2.1.1. Anti-Inflammatory Adipokines in MS

2.1.1.1. Adiponectin

Adiponectin is an anti-inflammatory adipokine. It is a peptide with a molecular weight of 30 kDa, primarily secreted by white adipose tissue [7]. Its actions include: a) suppression of NF-κB activity, b) reduction of TNF-α and IL-6 secretion from macrophages, c) decreased production of reactive oxygen species (ROS), d) reduced glucose levels in tissues, e) increased insulin secretion, f) inhibition of hepatic gluconeogenesis, g) cardioprotection, h) increased nitric oxide (NO) synthesis in the vascular endothelium, and i) promotion of angiogenesis [7] (Figure 2). Serum adiponectin levels are decreased in obesity, insulin resistance, type 2 diabetes (T2D), dyslipidemia, and cardiovascular diseases (CVDs) [7]. Moreover, its synthesis is inhibited by proinflammatory cytokines such as TNF-α and IL-6 [7]. In animal models, the absence of adiponectin in mice with experimental autoimmune encephalomyelitis (EAE) was found to result in enhanced lymphocyte activation and increased disease severity [35].
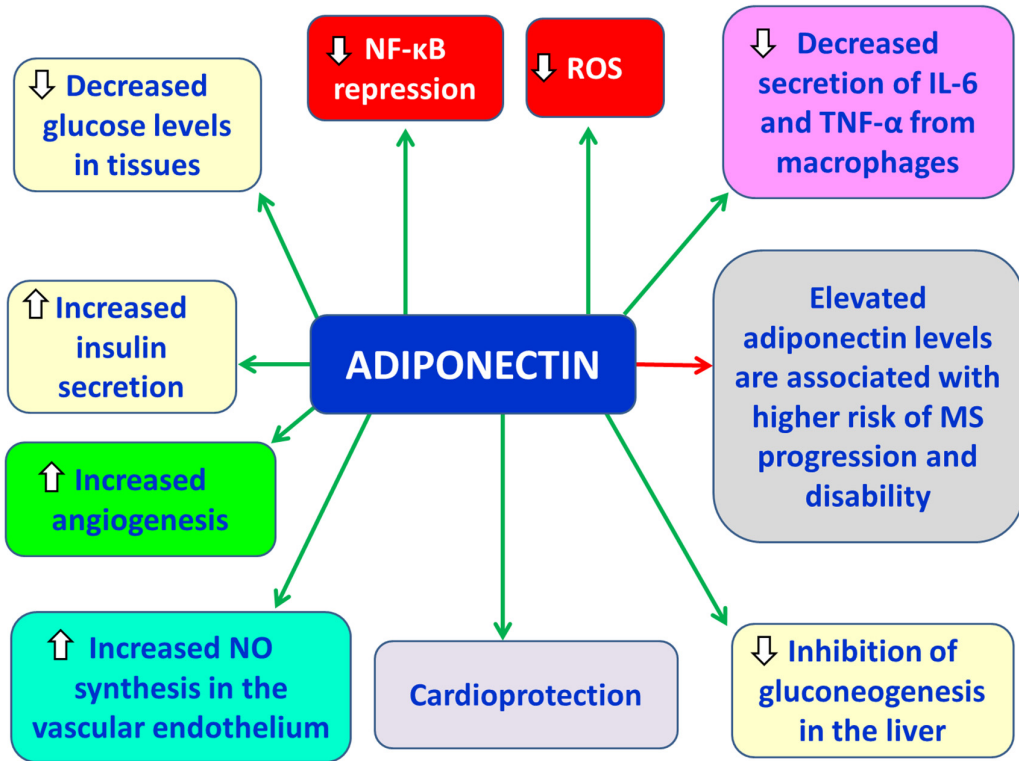
Figure 2. *Protective actions of adiponectin in obesity and its potential role as a biomarker for monitoring the progression and severity of multiple sclerosis (MS).* ROS: reactive oxygen species; NF-κB: nuclear factor kappa B; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; NO: nitric oxide; MS: multiple sclerosis.

Tehrani et al. reported elevated adiponectin levels in female patients with early-onset relapsing-remitting multiple sclerosis (RRMS) compared to healthy controls [36]. Similarly, Düzel et al. observed comparable findings [37]. Furthermore, higher serum adiponectin levels at the time of MS diagnosis—prior to any treatment—have been associated with an increased risk of disease progression and disability [38]. Signoriello et al. found elevated adiponectin concentrations in the cerebrospinal fluid (CSF) of patients with primary progressive MS (PPMS) compared to RRMS patients, with higher CSF adiponectin levels being correlated with greater Expanded Disability Status Scale (EDSS) scores at disease onset and more severe disease course after 4.5 years of follow-up [39]. Conversely, Musabak et al. reported lower adiponectin levels in MS patients [40], a finding that was also confirmed by Kraszula et al. [41]. Therefore, adiponectin may represent a valuable biomarker at the onset of MS, potentially aiding in predicting disease progression and severity [42].

2.1.1.2. Apelin

Apelin is a small molecular weight peptide classified among the anti-inflammatory adipokines and is primarily secreted by adipocytes [7]. Its main actions include a) promoting the differentiation and metabolic activity of brown adipocytes and inducing the browning of white adipose tissue, b) increasing glucose uptake by cells, c) enhancing insulin sensitivity, d) inhibiting lipogenesis, lipolysis, and fatty acid oxidation, e) promoting the synthesis of antioxidant enzymes, and f) reducing oxidative stress (OS) [7] (Figure 3). Serum levels of apelin have been found to be elevated in obesity, which may be attributed either to peripheral apelin resistance or to a compensatory mechanism aiming to counteract insulin resistance in peripheral tissues [7]. In in cellulo studies using N9 microglial cell lines, apelin suppressed LPS (lipopolysaccharide)-induced production of iNOS and IL-6, while upregulating IL-10 and arginase-1 [43].
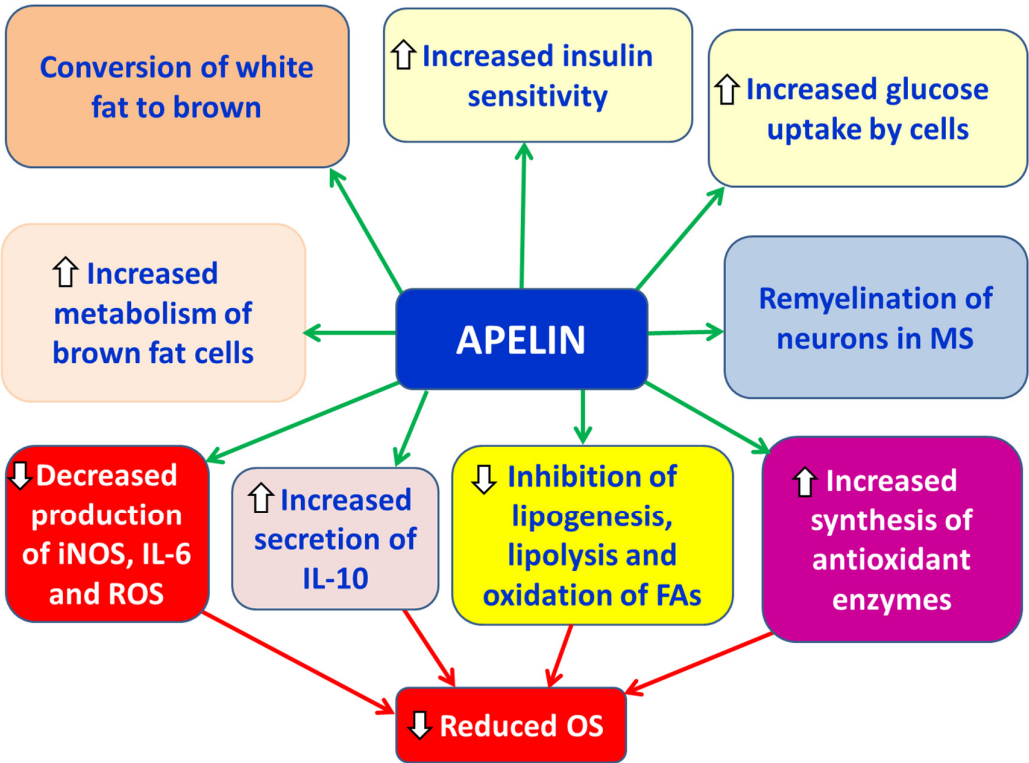
Figure 3. *Protective actions of apelin in obesity and its potency towards obesity-associated multiple sclerosis (MS). IL-6: interleukin-6; IL-10: interleukin-10; iNOS: inducible nitric oxide synthase; ROS: reactive oxygen species; OS: oxidative stress; FAs: fatty acids; MS: multiple sclerosis.*

Rasooli et al. reported significantly lower plasma apelin levels in MS patients compared to healthy controls, with a statistically significant negative correlation with Expanded Disability Status Scale (EDSS) scores and relapse rate [36]. Similarly, Tehrani et al. observed reduced apelin levels in the blood of women with very early-stage relapsing-remitting MS (RRMS), which were positively correlated with both EDSS scores and the number of relapses [36]. In contrast, Alpua et al. found elevated apelin levels in patients with RRMS compared to controls, though no correlation was found with disease severity or duration [44]. Apelin and its receptor, APJ, are widely expressed in the central nervous system (CNS), particularly in neurons and oligodendrocytes [45]. Activation of APJ has been shown to promote remyelination by modulating myelin-associated regulatory factors, especially in demyelinating conditions related to aging or experimental autoimmune encephalomyelitis (EAE) [46]. Furthermore, apelin appears to facilitate the differentiation of neural stem cells, suggesting a potential role in remyelination processes during the course of MS [47].

2.1.2. Proinflammatory Adipokines in Multiple Sclerosis (MS)

2.1.2.1. Leptin

Leptin is classified among the proinflammatory adipokines [48]. It is a peptide consisting of 167 amino acids with a molecular weight of 16 kDa [48]. Leptin is primarily secreted by white adipose tissue, and its circulating levels correlate directly with the mass of adipose tissue [49]. Its main functions include: (a) regulation of food intake and metabolism through communication with the central nervous system (CNS) via specific receptors [48], (b) upregulation of proinflammatory cytokines such as TNF-α and IL-6, and (c) promotion of the proliferation of proinflammatory Th1 and Th17 cells [50,51] (Figure 4). In obesity, leptin resistance occurs, resulting in elevated serum leptin levels [52], which may also be associated with alterations observed in the blood-brain barrier (BBB) of obese individuals [53]. Furthermore, increased leptin concentrations have been detected in the serum and cerebrospinal fluid (CSF) of patients with relapsing-remitting MS (RRMS) [54,55]. Ouyang et al. demonstrated in an experimental autoimmune encephalomyelitis (EAE) mouse model that removal of leptin receptors attenuated leukocyte infiltration into the CNS and reduced BBB disruption [56].
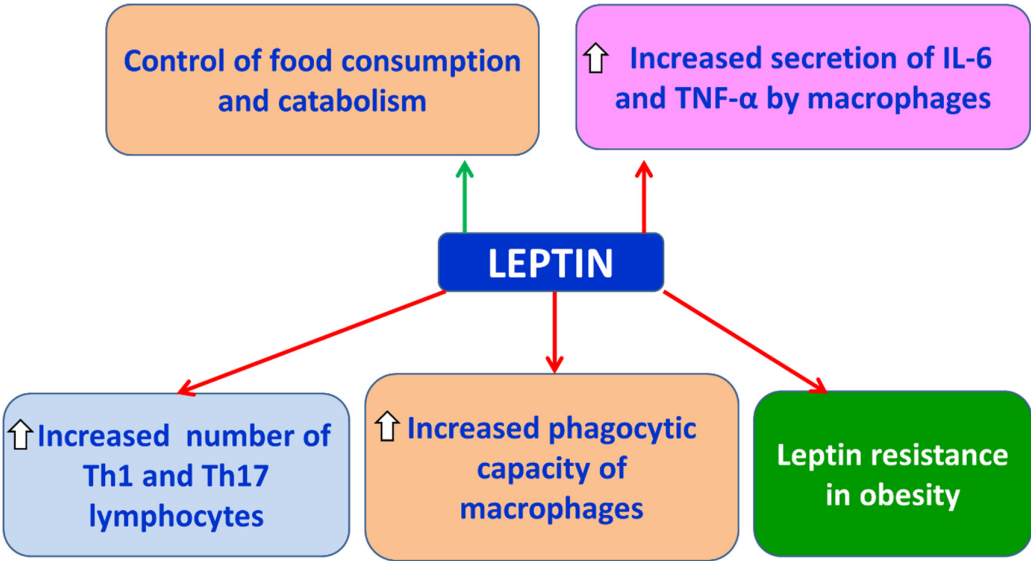
Figure 4. Actions of leptin related to the pathophysiology of multiple sclerosis (MS). *IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; Th1 lymphocytes: T helper 1 lymphocytes; Th17 lymphocytes: T helper 17 lymphocytes.*

2.1.2.2. Visfatin

Visfatin is a proinflammatory adipokine with a molecular weight of 52 kDa, secreted by macrophages in visceral adipose tissue, bone marrow, skeletal muscles, liver, lungs, pancreas, heart, brain, and various other organs [7]. Visfatin upregulates the expression of chemokines CCL2, CXCL2 (macrophage inflammatory protein 2α, MIP2-α), and CXCL8 (IL-8), as well as adhesion molecules such as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1), acting as a chemoattractant for monocytes and lymphocytes [57]. Moreover, it induces (a) the release of proinflammatory cytokines including IL-1β, IL-6, and TNF-α, (b) endothelial dysfunction via the NF-κB pathway, and (c) oxidative stress also through NF-κB signaling [7] (Figure 5). Elevated visfatin levels have been reported in obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), and cardiovascular diseases (CVDs), while weight reduction in obese patients has been shown to decrease visfatin concentrations [7]. In microglial cells, visfatin plays a facilitative role in promoting the production of proinflammatory mediators such as IL-1β, IL-6, inducible nitric oxide synthase (iNOS), nitric oxide (NO), and ROS in response to LPS stimulation [58]. In experimental autoimmune encephalomyelitis, pharmacological suppression of visfatin after the appearance of clinical symptoms leads to a marked reduction in neurological impairment and spinal cord demyelination [59]. Moreover, research by Emamgholipour et al. demonstrated that individuals with RRMS exhibited elevated visfatin concentrations compared to those with primary or secondary progressive MS (PPMS and SPMS), with visfatin levels showing a positive correlation with proinflammatory cytokines TNF-α and IL-1β [60].

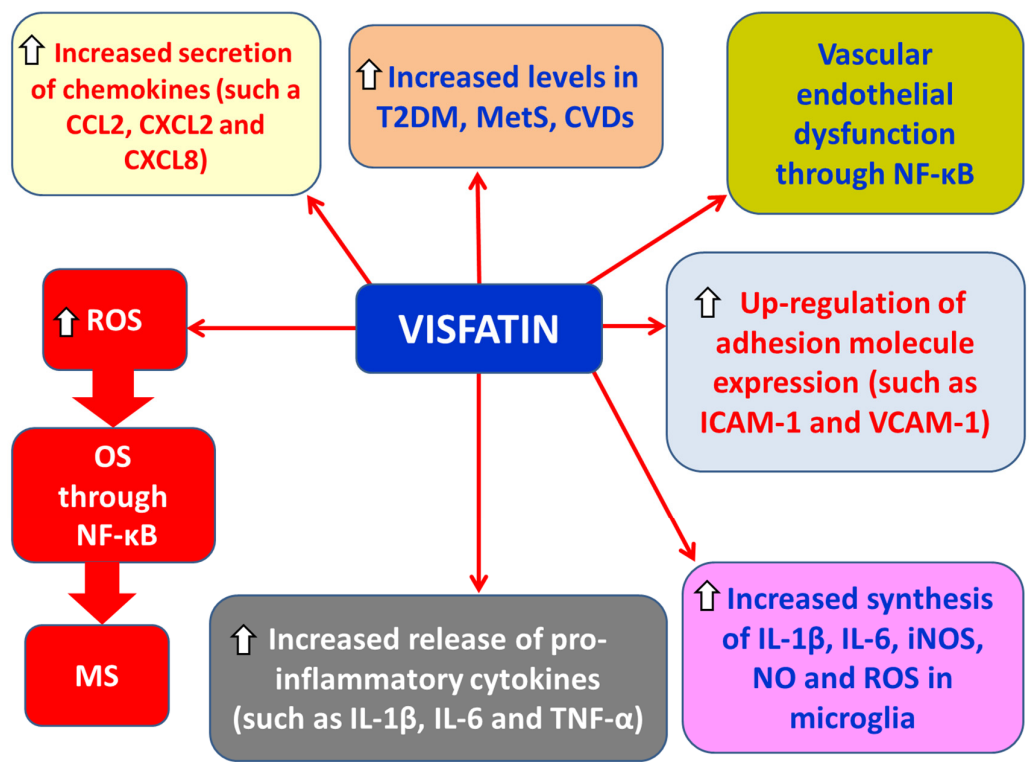**Figure 5.** Effects of visfatin on chronic inflammation and oxidative stress associated with obesity and multiple sclerosis (MS). CCL2: chemokine (C-C motif) ligand 2; CXCL2: chemokine (C-X-C motif) ligand 2; CXCL8: chemokine (C-X-C motif) ligand 8; T2DM: type 2 diabetes mellitus, MetS: metabolic syndrome; CVDs: cardiovascular diseases; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule-

1; ROS: reactive oxygen species; NF-κB: ; MS: multiple sclerosis; IL-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; NOS: ; NO: nitric oxide: nitric oxide synthase.

2.1.2.3. Resistin

Resistin is a proinflammatory adipokine with a molecular weight of 12.5 kDa, primarily secreted by macrophages within adipose tissue [7]. Resistin (a) promotes the activation of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, (b) upregulates several adhesion molecules, and (c) enhances oxidative stress (OS) [7]. Some studies have reported that elevated serum resistin levels are associated with obesity, insulin resistance, and type 2 diabetes mellitus (T2DM), while other studies have not confirmed these findings [7]. Additionally, Hossein-Nezhad and colleagues found increased serum resistin levels in patients with multiple sclerosis (MS) compared to controls, along with elevated levels of IL-1β, TNF-α, and C-reactive protein (CRP) [61]. Moreover, in patients with relapsing-remitting MS (RRMS), higher serum resistin levels correlated with reduced regulatory T cell (Treg) activity [41] (Figure 6).
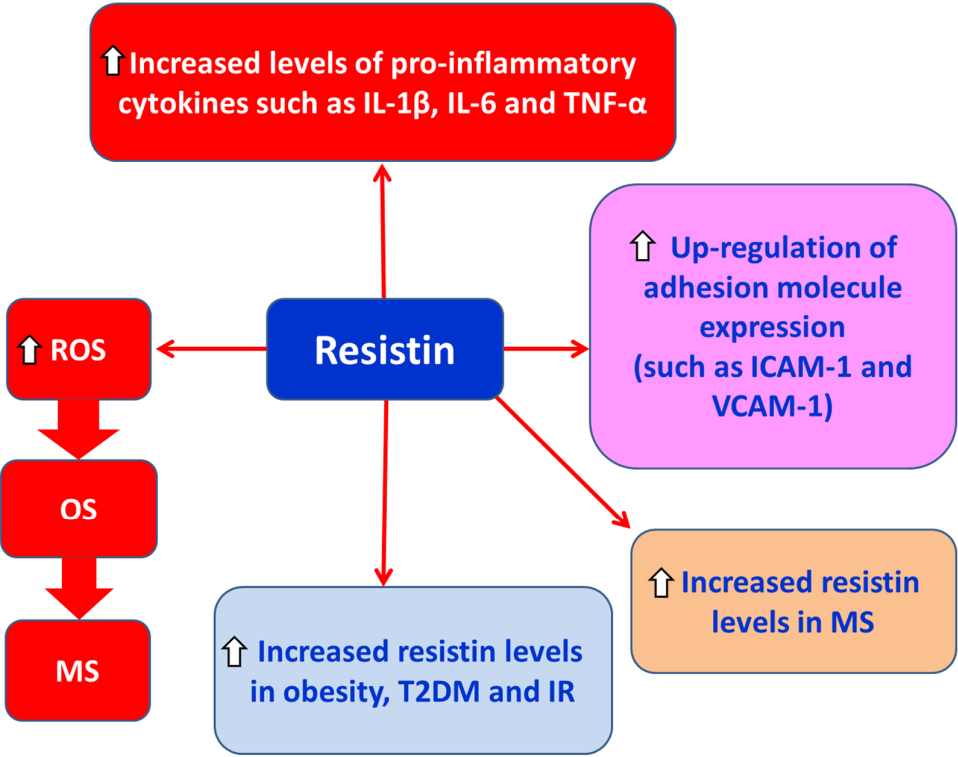

Figure 6. Actions of resistin in chronic inflammation and oxidative stress associated with obesity and MS. IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-alpha; ROS: reactive oxygen species; OS: oxidative stress; T2DM: type 2 diabetes mellitus; IR: insulin resistance; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule-1; MS: multiple sclerosis.

2.1.2.4. Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 is a physiological inhibitor of plasminogen activators (tPAs) [7,62,63]. Its increased activity is associated with impaired fibrinolysis and consequently a higher risk of cardiovascular diseases (CVDs) [7]. PAI-1 is secreted by adipose tissue, fibroblasts, vascular endothelial cells, and immune cells, and elevated serum levels have been observed in obese individuals, correlating with insulin resistance (IR), metabolic syndrome (MetS), and atherosclerosis [7]. Increased PAI-1 concentrations have also been detected in the serum and cerebrospinal fluid (CSF) of patients with MS [64].

Furthermore, serum PAI-1 levels were higher in active MS, compared to stable disease, and were positively associated with neurological deterioration and disability [64].

2.1.3.5. Chemerin

Chemerin is a proinflammatory adipokine that regulates adipocyte differentiation and is associated with obesity and MetS [65]. It acts as a chemoattractant for plasmacytoid dendritic cells (pDCs) and macrophages activated via Toll-like receptor 9 (TLR9) and high-mobility group box 1 protein (HMGB1), promoting type I interferon production [66]. Chemerin binds to the CCRL2 receptor (C-C chemokine receptor-like 2), facilitating macrophage infiltration and inducing IR [67]. In the central nervous system (CNS), chemerin is expressed by endothelial cells in MS sections and meninges, while its receptor CMKLR1 (chemokine-like receptor 1) is primarily found on infiltrating lymphocytes, dendritic cells, and macrophages [68]. Tomalka-Kochanowska et al. reported elevated chemerin levels in MS patients, correlating with obesity and increased body weight [69], whereas Koskderelioglu et al. did not observe similar findings [70], highlighting the need for further clinical investigations.

2.1.2.6. Fatty Acid Binding Protein 4 (FABP-4)

FABP-4 is a proinflammatory adipokine produced by adipocytes, monocytes, and macrophages, with its expression upregulated by Toll-like receptor 2 (TLR2) stimulation [71]. FABP-4 levels are higher in obese patients compared to overweight or normal-weight individuals [73]. Deficiency of FABP-4 reduces the secretion of proinflammatory cytokines via suppression of the NF-κB pathway [73], whereas administration of recombinant FABP-4 promotes proinflammatory cytokine secretion through the p38/NF-κB pathway [74]. Moreover, FABP-4 transports free fatty acids (FAs), released from lipolysis of fat droplets in the bloodstream, to various organs including the CNS [75,76]. FABP-4 knockout mice exhibit reduced clinical symptoms in experimental autoimmune encephalomyelitis (EAE) and decreased production of proinflammatory cytokines by dendritic cells [77,78]. In pediatric MS patients, a positive correlation between FABP-4, leptin, and relapsing-remitting MS (RRMS) has been observed, suggesting a potential role of these adipokines in disease progression [74]. Furthermore, in adult MS patients, FABP-4 has been associated with increased disability independently of body mass index (BMI) [72]. Similarly, in women, higher serum FABP-4 levels correlated with elevated Expanded Disability Status Scale (EDSS) scores [72]. Additionally, reduced expression of miR-34a has been detected in peripheral blood mononuclear cells (PBMCs) from patients with RRMS [79].

2.1.3. Pro-inflammatory Cytokines in MS

2.1.3.1. TNF-α

TNF-α is a proinflammatory adipokine primarily produced by macrophages, T and B lymphocytes, adipocytes, vascular endothelial cells, astrocytes, neurons, and muscles [7,80,81]. TNF-α exerts its effects through two distinct receptors, TNF-R1 and TNF-R2, which differ in their chemical affinity for TNF-α [7,81]. TNFR1 is expressed in all cell types [82], whereas TNFR2 is mainly found in neurons, endothelial cells, and various immune cells [83]. Expression of TNFR1 induces pathogenic effects, while TNFR2 expression has protective roles [84]. Specifically, soluble TNF-α mainly acts via TNFR1, mediating cellular apoptosis including oligodendrocytes [85] and chronic inflammation, whereas membrane-bound TNF-α acts primarily through TNFR2, activating genes involved in cell survival and resolution of inflammation [81]. It has been observed that in obesity and insulin resistance (IR), TNF-α expression is increased, with levels decreasing upon weight loss [7]. Experimental evidence also shows that TNF-α treatment increases IR in adipocytes [7]. TNF-α actions include: (a) stimulating MCP-1 (monocyte chemoattractant protein-1) and IL-6 secretion from preadipocytes [86], (b) inhibiting adiponectin synthesis [87], (c) increasing release of free fatty acids (FFAs) from adipocytes [87], (d) activating NF-κB, leading to elevated expression of adhesion

molecules on endothelial and vascular smooth muscle cells and promoting atherogenesis [87], (e) reducing insulin action on peripheral glucose uptake [7], (f) increasing lipolysis in adipocytes [7], and (g) promoting ROS and superoxide anion production, thereby causing OS [7] (Figure 7). TNF-α appears to be involved in MS activation [88,89]. Sharief and Henges reported increased TNF-α levels in active MS [90]. Moreover, elevated TNF-α levels in cerebrospinal fluid (CSF) correlated with MS severity and progression [90]. Single nucleotide polymorphisms (SNPs) in the TNFR1 gene (TNFRSF1A) have been linked to increased MS risk [91]. TNF-α is upregulated in mice with EAE, and TNF-α administration worsens disease progression in these mice [89,92,93]. Additionally, mice with EAE lacking TNFR1 are either fully resistant or develop milder disease [94,95]. Selective TNFR1 blockade improves EAE outcomes, while TNFR2 deficiency worsens EAE [96–98].
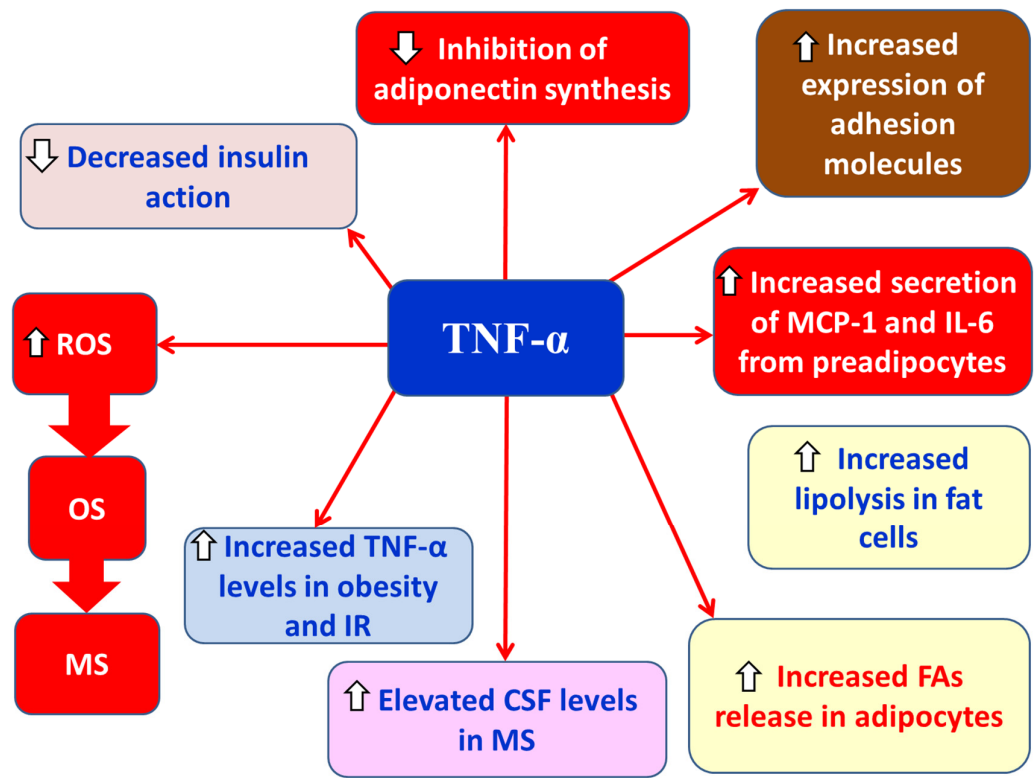

Figure 7. Actions of TNF-α in chronic inflammation and oxidative stress associated with obesity and MS. ROS: reactive oxygen species; OS: oxidative stress; MS: multiple sclerosis; TNF-α: tumor necrosis factor-alpha; IR: insulin resistance; IL-6: interleukin-6; MCP-1: monocyte chemo-attractant protein-1; FAs: fatty acids.

2.1.3.2. IL-6

Interleukin-6 (IL-6) is a proinflammatory cytokine that induces the acute phase response of inflammation [7,99,100]. It is secreted by various cell types, including adipocytes, endothelial cells, monocytes, T and B lymphocytes, fibroblasts, microglia, neurons, and pancreatic beta cells [7,99,100]. IL-6 signals either by binding to its alpha receptor IL-6Rα (classical signaling) or through binding to a soluble IL-6 receptor form (sIL-6R) [7,99]. IL-6 signaling via gp130 (glycoprotein 130) activates the JAK1/STAT3 pathway (janus kinase 1/signal transducer and activator of transcription 3), resulting in gene transcription [99]. IL-6 also activates the MAPK (mitogen-activated protein kinase) pathway, leading to transcription of additional genes [99]. Obese patients exhibit higher serum IL-6 levels, as do patients with chronic inflammatory diseases and abnormal blood lipid profiles [63,101]. Furthermore, one-third of circulating IL-6 is produced by adipose tissue [63,101]. The hypothalamus shows the highest expression of IL-6 receptors, suggesting IL-6's possible involvement in appetite and food intake regulation [63,101]. IL-6 appears to contribute to inflammation linked to MS

pathogenesis [99]. It also promotes Th17 lymphocyte development [99], while IL-6-deficient mice display resistance to EAE [102,103].

2.1.3.3. IL-8

Interleukin-8 (IL-8) is a proinflammatory cytokine mainly produced by monocytes and macrophages [101]. Oxidized LDL (oxLDL) promotes IL-8 production and release from macrophages derived from human atherosclerotic plaques and foam cells [101]. IL-8 also induces matrix metalloproteinase-9 (MMP-9) release from neutrophils [104]. Elevated IL-8 levels are found in obese patients and those with T2DM and MetS [105,106]. IL-8 is responsible for BBB disruption and immune cell migration into the CNS, with lower IL-8 levels in blood serum and higher levels in CSF of MS patients compared to healthy controls [107]. Lund et al. demonstrated significantly higher serum IL-8 in untreated MS patients compared to controls, which significantly decreased following interferon-beta-1a therapy [108]. Neuteboom et al. found that elevated IL-8 during pregnancy correlated with increased risk of postpartum relapse [109].

2.1.3.4. IL-18

Interleukin-18 (IL-18), also known as interferon-gamma (IFN-γ) inducing factor, is produced by hematopoietic and non-hematopoietic cells such as monocytes, macrophages, keratinocytes, and mesenchymal cells [110]. IL-18 belongs to the IL-1 cytokine family, which comprises 11 cytokines that promote innate immune system activity [110]. IL-18 stimulates both innate and adaptive immunity [110] and is implicated in MS and EAE development [111]. Increased IL-18 expression has been found in serum and peripheral blood mononuclear cells (PBMCs) of MS patients and in brain and spinal cord tissues of mice with EAE [112,113]. IL-18 binds to the IL-18 receptor (IL-18R) to exert proinflammatory effects by activating NF-κB signaling and promoting Th1 differentiation, leading to IFN-γ induction. However, the precise mechanisms by which IL-18 regulates MS and EAE progression still remain unclear [111,114,115].

2.1.3.5. IL-1β

Interleukin-1 beta (IL-1β) is a proinflammatory cytokine secreted by M1 macrophages [7]. Its roles in obesity include (a) promoting ectopic fat accumulation, (b) increasing blood glucose levels, (c) disrupting insulin secretion, (d) causing insulin resistance, (e) inducing T2DM, (f) forming atherosclerotic plaques, (g) causing hepatic steatosis, (h) promoting liver cirrhosis, (i) suppressing PPARγ expression, (j) increasing cytokine and chemokine expression, and (k) inducing oxidative stress [7] (Figure 8). IL-1β mediates neuroinflammation by promoting innate immune responses during MS pathophysiology [116]. In EAE or MS progression, a characteristic feature is BBB and blood-spinal cord barrier (BSCB) leakage, leading to IL-1β release and subsequent neuroinflammation [117–119]. Mice deficient in IL-1β or IL-1 receptor (IL-1R) are resistant to EAE [120,121]. The exact mechanism of IL-1β's role in EAE or MS is unclear, but IL-1β appears to promote differentiation of autoimmune CD4+ T cells into pathogenic Th1 and Th17 phenotypes, especially Th17 cells that express high IL-1R levels, thereby contributing to neuroinflammation and MS pathogenesis and clinical progression [119].

2.1.4. Anti-Inflammatory Cytokines in MS

2.1.4.1. IL-10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that plays a critical role in preventing inflammatory and autoimmune pathological conditions [122]. IL-10 is mainly produced by activated myeloid cells and lymphocytes, and to a lesser extent by other cells during inflammation [123]. IL-10 dimerizes and binds to the extracellular domain of two IL-10R1 subunits of the IL-10 receptor complex [123]. The IL-10 receptor complex is a tetramer consisting of two IL-10R1 subunits and two IL-10R2 subunits [123]. The IL-10R1 subunit is associated with JAK1 (Janus kinase 1), while the IL-

10R2 subunit is associated with TYK2 (tyrosine kinase 2) [123]. Activation of the IL-10 receptor complex induces phosphorylation and activation of STAT1 (Signal Transducer and Activator of Transcription 1), STAT3, STAT5, and SOCS1/3 (Suppressor of Cytokine Signaling 1 and 3), ultimately leading to the inhibition of NF-κB-mediated signaling [123]. IL-10 suppresses the production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-18, and TNF-α, while promoting the production of other anti-inflammatory mediators, such as IL-1β receptor antagonist [123]. The anti-inflammatory effects of IL-10 have been demonstrated in experimental models of multiple sclerosis (MS), where it attenuates neuroinflammation [123,124]. In EAE (experimental autoimmune encephalomyelitis) mouse models, IL-10-deficient mice developed more severe disease compared to wild-type mice, whereas those overexpressing IL-10 were resistant to EAE [125,126].
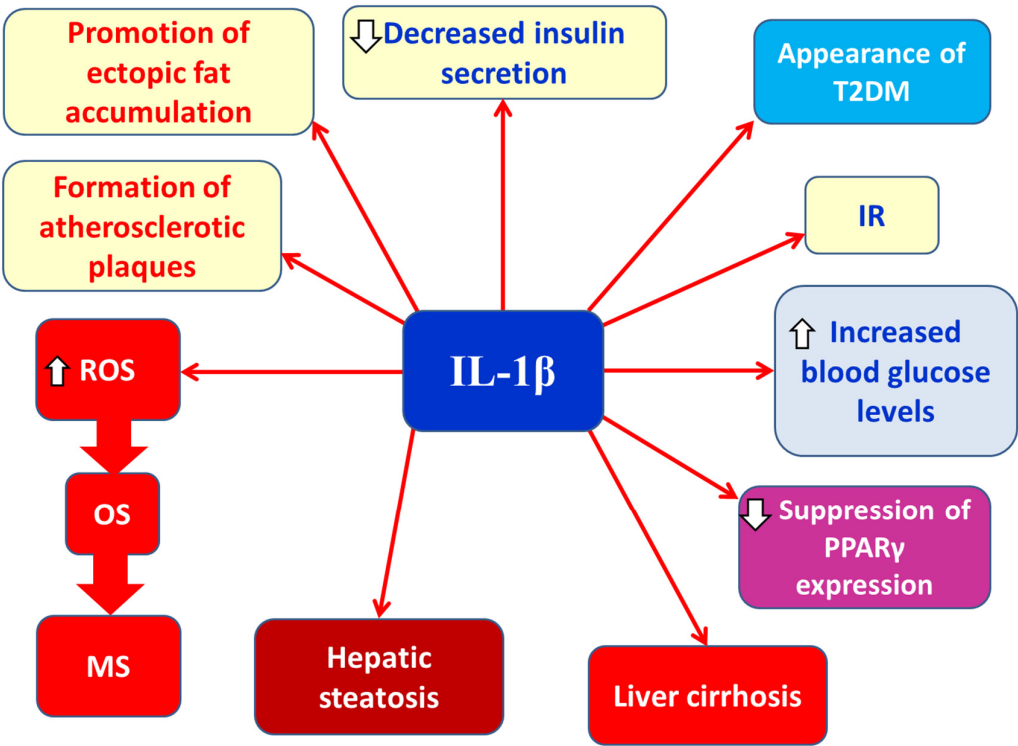

Figure 8. Actions of IL-1β in chronic inflammation and OS associated with obesity and MS. IL-1β: interleukin-1β; ROS: reactive oxygen species; OS: oxidative stress; MS: multiple sclerosis; IR: insulin resistance; PPARγ: peroxisome proliferator-activated receptor gamma.

2.2. Activation of the NLRP3 Inflammasome in Obesity and MS

Inflammasomes are large cytoplasmic multiprotein complexes that exert their effects through pattern recognition receptors (PRRs), promoting the secretion of mature pro-inflammatory cytokines IL-1β and IL-18 involved in inflammatory processes [25,127]. Inflammasomes consist of three components: (a) a sensor protein, such as the NOD-like receptor (NLR) family; (b) an adaptor protein (ASC or PYCARD, an apoptosis-associated protein containing a caspase recruitment domain); and (c) caspase-1 [128]. Toll-like receptors (TLRs) and NLRs are members of the PRR family, recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), respectively [128]. PRR activation initiates inflammasome assembly and triggers NF-κB activation. The adaptor protein ASC links the sensor protein (NLR) with caspase-1 [128]. Activation of the NLRP3 inflammasome occurs when PAMPs or DAMPs bind to NLR receptors due to various metabolic abnormalities, including lysosomal disruption, release of mitochondrial DNA (mtDNA), ROS, and elevated intracellular calcium levels (Ca²⁺) [128]. Subsequent NLR oligomerization occurs

via interactions of their PYD (pyrin domain) or CARD (caspase recruitment domain), followed by activation of caspase-1, which then leads to the production and secretion of mature IL-1β and IL-18 [128]. Activation of caspase-1 triggers pyroptosis programmed cell death [128].

NLRP3 inflammasomes are part of the NLR family and contain a leucine-rich repeat (LRR) domain, a nucleotide-binding site (NBS), and a pyrin domain-containing component (PDC-3) [128]. Esser et al. found increased expression of NLRP3 and IL-1β in macrophages infiltrating visceral fat of obese individuals with MetS compared to obese individuals without MetS [129]. In obesity, NLRP3 inflammasomes are activated by an excess of metabolic DAMPs such as ATP, glucose, fatty acids, ceramides, oxidized low-density lipoproteins (ox-LDL), crystallized uric acid, cholesterol crystals, and monosodium urate. Moreover, pro-inflammatory adipokines, like leptin, resistin, and TNF-α, contribute to NLRP3 activation, leading to caspase-1-mediated secretion of mature IL-1β and IL-18 [16,130]. Palmitic acid, a saturated fatty acid, activates the NLRP3-PYCARD inflammasome via mitochondrial ROS, AMPK (AMP-activated protein kinase), and the autophagy signaling cascade involving ULK1 (UNC-51-like kinase), resulting in caspase-1, IL-1β, and IL-18 production. This suggests a connection between high-fat diets and inflammation [131]. Conversely, oleic acid, an unsaturated fatty acid, inhibits palmitic acid's effects by promoting AMPK activation and reducing endoplasmic stress (ER stress) [132]. Similarly, long-chain polyunsaturated fatty acids (PUFAs), such as omega-3s, inhibit caspase-1 activation through their receptor GPR120 (G-protein-coupled receptor 120). GPR120 binds to β-arrestin-2, forming a complex that interacts with and inhibits NLRP3 inflammasome activation [133]. In contrast, cholesterol crystals activate the NLRP3 inflammasome through lysosomal membrane rupture [134], and ox-LDL via NF-κB activation [135]. Hyperglycemia can also stimulate NLRP3 inflammasome activation in human adipose tissue through upregulation of TXNIP (thioredoxin-interacting protein), resulting in elevated IL-1β expression and contributing to the development of insulin resistance (IR) [136]. Increased glutamate levels during glucose deprivation and hypoxia induce endoplasmic reticulum stress (ER stress), elevated intracellular calcium (Ca^{2+}), and upregulation of TXNIP expression [137]. Lipopolysaccharides (LPS) are potent PAMPs that act as endotoxins. Their levels increase in conditions like obesity and T2DM due to altered gut microbiota and increased intestinal permeability. LPS are taken up by macrophages and adipocytes and activate NLRP3 inflammasomes, leading to the production of pro-IL-1β via TLR4- and NF-κB-dependent pathways and the initiation of inflammatory responses [138]. Additionally, ATP, beyond its role as an intracellular energy carrier, is a major NLRP3 inflammasome activator via the NF-κB pathway [139]. NLRP3 inflammasomes are involved in the pathophysiology of MS [25]. Elevated expression levels of NLRP3 and IL-1β have been found in MS lesions [140,141], together with increased ASC, caspase-1, and IL-18 at the serum [140,141]. In EAE mouse models, elevated expression of NLRP3 mRNA and protein levels has been reported [111,142]. Additionally, Nlrp3$^{-/-}$ mice showed reduction of Th1 and Th17 lymphocytes in the spinal cord and peripheral lymphoid tissues, as well as significantly milder EAE symptoms compared to wild-type mice [111,143]. Moreover, Yu et al. showed that mice lacking thymic stromal lymphopoietin (TSLP) (Tslpr$^{-/-}$ mice) exhibited decreased NLRP3 expression and lower EAE scores [144].

2.3. Gut Microbiota Dysbiosis in Obesity and Multiple Sclerosis (MS)

Significant differences have been observed between the gut microbiota of obese individuals and that of people with normal body weight [16], which are attributed to alterations in the composition and function of the host microbiome [145]. The gut microbiota of obese individuals has the capacity to increase intestinal and blood–brain barrier (BBB) permeability [16,146,147]. Thus, in obese patients, lipopolysaccharides (LPS) from the outer membrane of Gram-negative bacteria, produced following fermentation, translocate across the intestinal mucosa and cross the BBB, acting on astrocytes and microglia [146–150], thereby altering the Treg/Th17 cell ratio in the central nervous system (CNS) and promoting neuroinflammation [151]. In obesity, there is an abundance of certain bacterial species (e.g., Archaea), along with a decrease or absence of other groups such as the Firmicutes and Bacteroidetes phyla [152]. The presence of certain bacteria in the gut microbiota of patients with MS,

such as Fusobacteria, has been associated with an increased risk of disease relapse [153]. Therapeutic approaches in MS patients using probiotics and fecal microbiota transplantation aimed at modifying the gut microbial ecosystem have not yielded promising results to date [154]. Furthermore, it has been observed that MS patients exhibit low levels of propionic acid in both feces and blood [155]. Exogenous administration of propionic acid as adjunct therapy in MS was found to significantly reduce Th1 cell activity and enhance Treg cell function, resulting in less disability and fewer disease relapses [155].

3. Oxidative Stress (OS) in Obesity and Multiple Sclerosis

Oxidative stress (OS) in obesity arises through two main pathways. The first involves chronic inflammation in adipose tissue, where overproduction of proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, stimulates mitochondrial and peroxisomal oxidative phosphorylation, resulting in the generation of free radicals (FRs), mitochondrial DNA damage, ATP depletion, and lipotoxicity [7,60]. Chronic inflammation is further exacerbated by activation of PGE2 (prostaglandin E2), COX-2 (cyclooxygenase-2), and MAPK pathways [156]. Moreover, in obesity there is reduced expression of PPAR-γ by fatty acids and their metabolites. As a result, PPAR-γ fails to upregulate antioxidant genes and downregulate proinflammatory mediators [157]. The second pathway of OS involves the formation of NADPH oxidases, both through the pentose phosphate pathway signaling mechanism and the increased expression of NADPH oxidases in macrophages [156]. These enzymes catalyze the transfer of electrons from NADPH, reducing oxygen and generating the $O_2^{\bullet-}$, which is subsequently reduced to H_2O_2 [156]. H_2O_2 is then broken down into water and oxygen by antioxidant enzymes such as catalase (CAT) and glutathione peroxidase (GPx). In cases of antioxidant enzyme deficiency, reactive oxygen species (ROS) accumulate [156,158]. Thus, ROS overproduction in obesity results from both NADPH oxidase activity and mitochondrial oxidative phosphorylation. Within mitochondria, molecular oxygen (O_2) is reduced to H_2O through the flavin mononucleotide and ubiquinone cycle, producing both superoxide anions ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) [159]. The excessive generation of ROS leads to oxidative stress. In OS, increased levels of malondialdehyde (MDA), a biomarker of cellular damage and lipid peroxidation, are also observed [156].

Similarly, in MS, neuroinflammation activates the MAPK (p38 mitogen-activated protein kinase) signaling pathway in the nuclei of macrophages and dendritic cells, resulting in overproduction of proinflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-12, IL-6, and IL-23 [160]. Moreover, activation of the transcription factor NF-κB in CNS cells, including T lymphocytes, macrophages, microglia, astrocytes, and oligodendrocytes, enhances neuroinflammation and drives MS pathogenesis [161]. Neuroinflammation also activates JNK signaling, leading to demyelination and neuronal apoptosis [162], and disrupts the PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase B) pathway, contributing to MS exacerbation [163]. Neuroinflammation induces the overproduction of ROS and nitric oxide (NO) by glial cells and activates the arachidonic acid pathway in the CNS via COX and lipoxygenase (LOX), triggering OS [164,165]. OS can damage DNA, lipids, and proteins in neurons, leading to cell death [166]. It can also impair mitochondrial function and sodium-potassium pump activity, reducing ATP production, causing potassium accumulation, and inducing apoptosis [167]. Furthermore, ROS and nitric oxide synthase (NOS) overproduction in neural cells damages the myelin sheath and disrupts the integrity of the BBB [168–170].

Figure 9 schematically illustrates the interplay among obesity, chronic inflammation, oxidative stress (OS), and MS pathogenesis, highlighting the following: OS in obesity arises via two mechanisms. The first stems from chronic adipose tissue inflammation, which through excessive secretion of proinflammatory cytokines like TNF-α, IL-6, and IL-1β, triggers mitochondrial and peroxisomal oxidative phosphorylation, leading to ROS production. Chronic inflammation is further exacerbated by activation of PGE2, COX-2, and MAPK. In addition, obesity is associated with reduced expression of PPAR-γ by fatty acids and their metabolites, limiting the upregulation of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. The second mechanism involves NADPH oxidase formation. These enzymes transfer electrons from NADPH to

oxygen, generating superoxide ($O_2^{\bullet-}$), which is then converted to hydrogen peroxide (H_2O_2). H_2O_2 is subsequently broken down into H_2O by antioxidant enzymes such as CAT and GPx. In the absence of sufficient antioxidant defenses, ROS accumulate. Thus, ROS overproduction in obesity stems from both NADPH oxidases and mitochondrial oxidative phosphorylation. The resulting oxidative stress (OS) is marked by elevated MDA levels and increased peroxidized lipid ratios, promoting chronic low-grade inflammation. OS also promotes further activation of PGE2, COX-2, and MAPK, reinforcing inflammation. Both chronic inflammation and OS contribute to the pathogenesis of MS.
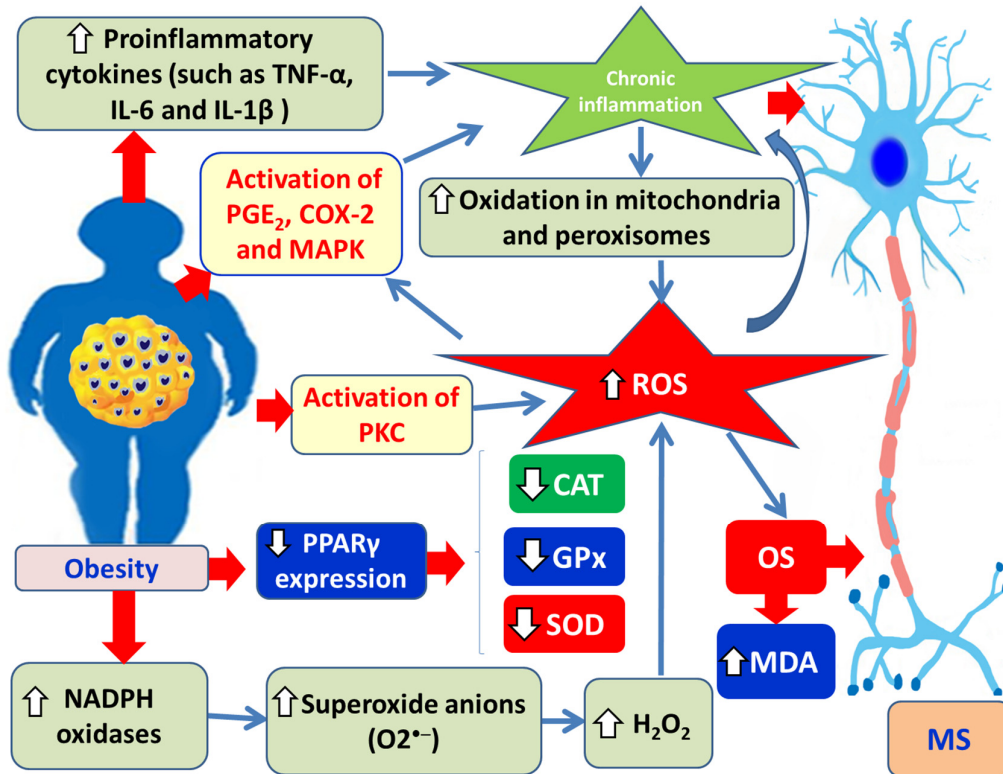

Figure 9. Schematic representation of the interaction between obesity, chronic inflammation, and oxidative stress in the pathogenesis of multiple sclerosis (MS). ROS: reactive oxygen species; PGE2: prostaglandin E2; COX-2: cyclooxygenase-2; MAPK: mitogen-activated protein kinase; PPAR-γ: peroxisome proliferator-activated receptor gamma; NADPH: nicotinamide adenine dinucleotide phosphate; MDA: malondialdehyde; PKC: protein kinase C.

4. Antioxidant Compounds in the Management of Multiple Sclerosis

A key regulator of the antioxidant response is Nrf2 (nuclear factor erythroid 2-related factor 2) [171]. Under normal conditions, Nrf2 is bound to the Keap1 protein in the cytoplasm, which signals its degradation via the ubiquitin-proteasome system [171]. Under oxidative stress (OS), Nrf2 dissociates from Keap1 (Kelch-like ECH-associated protein 1) and translocates to the nucleus, where it binds to antioxidant response elements (AREs) and induces the transcription of target genes encoding antioxidant enzymes and detoxification proteins, thereby protecting cells from the damaging effects of reactive oxygen species (ROS) and maintaining redox homeostasis [172]. The Nrf2 signaling pathway is a promising target for activating antioxidant mechanisms in MS, as it regulates the expression of several antioxidant enzymes [173]. Moreover, the JNK and ERK signaling pathways can phosphorylate Nrf2 and promote its nuclear translocation [174,175]. There are two endogenous antioxidant defense systems, enzymatic antioxidants, such as glutathione peroxidase, catalase, superoxide dismutase (SOD), and paraoxonase 2 (PON2), and free radical scavenging molecules, such as alpha-tocopherol (vitamin E) and glutathione [164,176]. Some of the enzymes

regulated by Nrf2 include superoxide dismutase (SOD), heme oxygenase-1 (HO-1), glutathione peroxidases (GPxs), and catalase [172]. Catalase is a first-line defense enzyme against ROS and OS [172]. Gray et al. found increased catalase expression in the gray matter of MS patients compared to controls, suggesting an attempt by the enzyme to neutralize oxidative stress [177]. Similarly, SOD acts as a primary defense against OS, and reduced SOD activity has been associated with uncontrolled ROS production [172]. Obradovic and colleagues reported elevated SOD activity in the serum of MS patients, confirming oxidative and inflammatory injury in MS [178]. In addition, the coenzyme CoQ10 may exert dose-dependent beneficial effects on improving OS and inflammation in MS [179]. Furthermore, several non-enzymatic compounds, such as polyunsaturated fatty acids, glutathione, N-acetylcysteine, alpha-lipoic acid, melatonin, L-carnitine, and various polyphenols (e.g., epigallocatechin, quercetin, curcumin, and resveratrol), have shown beneficial effects against obesity-related metabolic disorders [180] and may serve as adjunct therapies in MS [181]. Likewise, trace elements such as iron (Fe), zinc (Zn), manganese (Mn), and copper (Cu) exhibit beneficial effects on metabolic disorders related to obesity [179] and may play a supportive role in MS treatment [181]. Additionally, targeting inflammatory mediators represents an alternative therapeutic strategy for MS. However, the safety and efficacy of such interventions must be further studied and validated in future clinical trials. Anti-inflammatory compounds that interfere with inflammatory mediators include: a) IL-1R antagonists [7,182], b) recombinant anti-IL-1β antibodies [7], c) NF-κB inhibitors [7], d) anti-TNF-α agents [7], e) inflammasome-targeting compounds [127,183–185], and f) thiazolidinediones, which act as potent and selective activators of PPAR [7,183–185]. Finally, anti-obesity drugs with anti-inflammatory and antioxidant potential could prove useful as adjunct therapies in the management of MS [186].

4.1. Antioxidants as Complementary Therapy in MS

4.1.1. Vitamin D

Vitamin D reduces the number of activated autoreactive T lymphocytes in the CNS [187], which attack the myelin sheath and contribute to the pathogenesis of multiple sclerosis (MS) [188]. It also appears to inhibit the differentiation of dendritic cells [189,190], which are innate immune cells involved in MS pathogenesis [191]. Furthermore, vitamin D reduces the accumulation of macrophages in the CNS in experimental autoimmune encephalomyelitis (EAE) models, indicating potential neuroprotective effects [192–195]. In parallel, vitamin D enhances the activity of regulatory T cells (Tregs) [196], which suppress autoreactive T lymphocytes of the immune system [197]. Additionally, vitamin D induces a shift from Th1 toward Th2 cells [198], thereby promoting a shift in T-cell-derived cytokine production from pro-inflammatory Th1 cytokines, such as TNF-α, IFN-γ, and IL-2 [207], to anti-inflammatory Th2 cytokines, including IL-4, IL-5, and IL-10 [199]. Moreover, vitamin D reduces the production of nitric oxide (NO) [200] and suppresses the inducible nitrogen monoxide synthase (iNOS) pathway [201] in microglia, macrophages, and astrocytes [202]. This is particularly important, as NO contributes to BBB disruption, damage of oligodendrocytes and axons, and demyelination [203]. Overall, vitamin D plays a protective role in the onset of MS, reduces disease severity, and decreases the frequency of relapses [204,205] (Figure 10).

4.1.2. Vitamin A

Vitamin A, particularly through its active metabolite retinoic acid, enhances the integrity of the blood–brain barrier (BBB) [206], thereby restricting the passage of peripheral pro-inflammatory substances and immune cells into the brain parenchyma [181,207]. In addition, vitamin A exerts anti-inflammatory and antioxidant properties in the CNS [181,208]. It inhibits the secretion of pro-inflammatory cytokines such as IL-1, IL-12, TNF-α, and nitric oxide (NO) [181,209]. Vitamin A also increases the secretion of the anti-inflammatory cytokine IL-10 by B cells in MS and simultaneously enhances the production of antioxidant enzymes, thereby protecting the brain from oxidative stress [181,210]. Furthermore, it activates PPARs, modulating the phenotype of CNS macrophages, reducing neuroinflammation, neuronal oxidative stress, and axonal demyelination [181].

Additionally, vitamin A inhibits the transcription factor NF-κB and the activator protein 1 (AP-1), both involved in T cell activation, as well as STAT-1, which plays a role in neuroinflammation [181,211]. Vitamin A also promotes the differentiation of T cells into Th2 to produce anti-inflammatory cytokines [181,212]. Likewise, it increases the number of regulatory T cells (Tregs), which suppress autoreactive T lymphocytes of the immune system that attack the myelin sheath and contribute to MS pathogenesis [181,213]. At the same time, vitamin A inhibits the differentiation of CD4+ T cells into Th1 and Th17, thereby protecting against neuroinflammation [181,213] (Figure 11). Similarly, vitamin A suppresses the ability of CD4+ T cells to induce EAE and plays a protective role in the onset of MS [181,213].
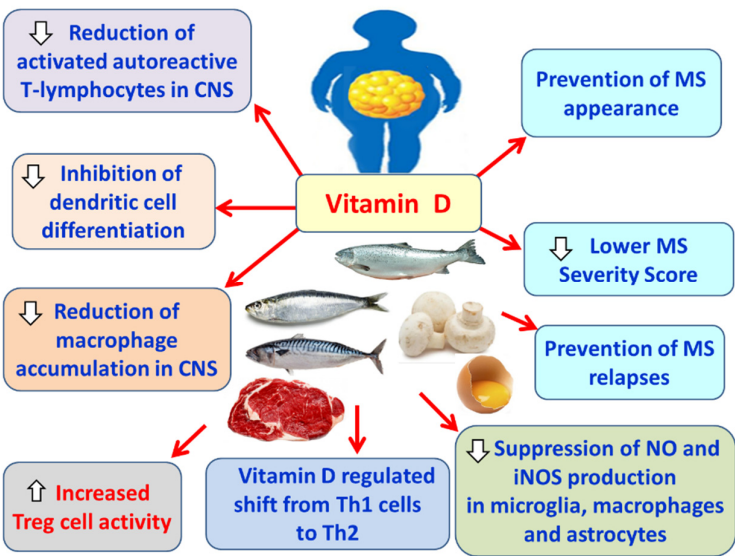

Figure 10. Schematic representation of the beneficial effects of vitamin D against MS. CNS: central nervous system; Treg cell: regulatory T cell; Th1 cell: T helper 1 cell; Th2 cell: T helper 2 cell; NO: nitrogen oxide; iNOS: inducible nitric oxide synthase; MS: multiple sclerosis.
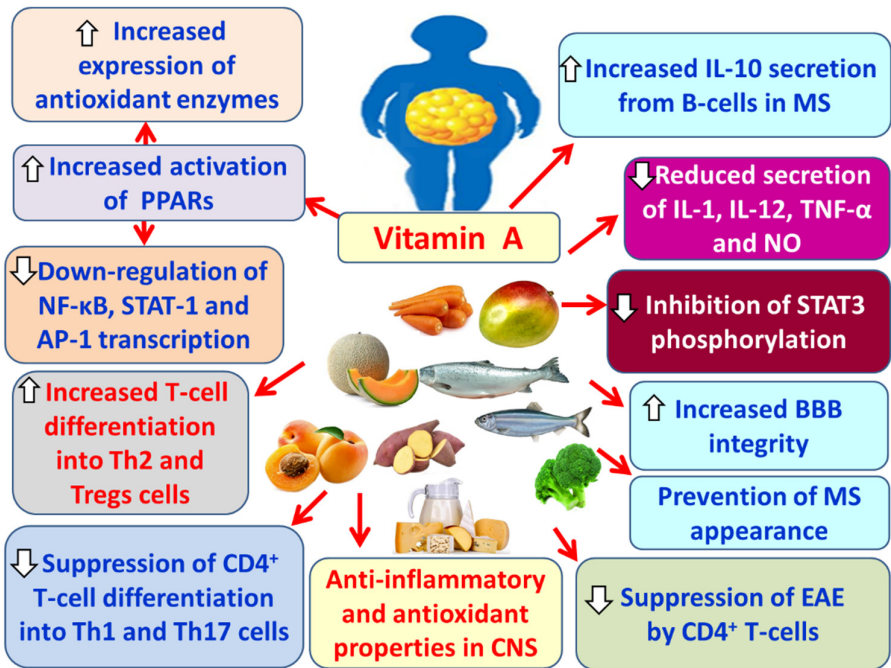

Figure 11. Schematic representation of the beneficial effects of vitamin A against multiple sclerosis (MS). PPARs: peroxisome proliferation-activated receptor; NF-κB: nuclear factor-κB; STAT-1: signal trasducer and activator of

transcription 1; AP-1: activator protein 1; CD4+ T lymphocytes: also known as helper T cells; Th1 cell: T helper 1 cell; Th17 cell: T helper 17 cell; CNS: central nervous system; BBB: blood-brain barrier; IL-1: interleukin-1; IL-12: interleukin ; TNF-α: tumor necrosis factor-alpha; STAT3: signal transducer and activator of transcription 3; MS: multiple sclerosis.

4.1.3. Curcumin

Curcumin has the ability to cross the blood–brain barrier (BBB) and protect the brain from inflammatory damage [214,215]. It prevents the degradation of tight junction proteins of the BBB [216], thus preserving the barrier's integrity and limiting the entry of peripheral immune cells and inflammatory mediators into the brain parenchyma [181]. Moreover, curcumin has been shown to promote remyelination of neurons in animal models of MS [217]. It also exerts anti-inflammatory and antioxidant properties in the CNS, promotes the clearance of ROS, and chelates metal ions such as manganese, iron, copper, and zinc [181,218,219]. Additionally, curcumin inhibits the expression of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-17, and TNF-α in the CNS, as well as the expression of COX-2, MCP-1, and macrophage inflammatory protein-1α (MIP-1α) [220,221]. Curcumin also inhibits the activation of NF-κB, thereby suppressing the pro-inflammatory responses involved in the pathogenesis of both MS and EAE [181]. Likewise, it inhibits the differentiation of Th17 cells, which play a key role in MS pathogenesis [222]. Furthermore, curcumin restores the function of Tregs [223], which suppress the autoreactive T lymphocytes that attack the myelin sheath and contribute to MS development [224]. Curcumin also activates Nrf2, resulting in protection against oxidative stress, mitochondrial dysfunction, neuroinflammation, and neurodegeneration in MS [218,225]. Additionally, curcumin exerts neuroprotective effects in neurodegenerative diseases by activating antioxidant systems, such as heat shock proteins 70 (Hsp70s), heme oxygenase-1 (HMOX-1), and thioredoxin, which is essential for maintaining mitochondrial ROS homeostasis [215,225,226] (Figure 12).
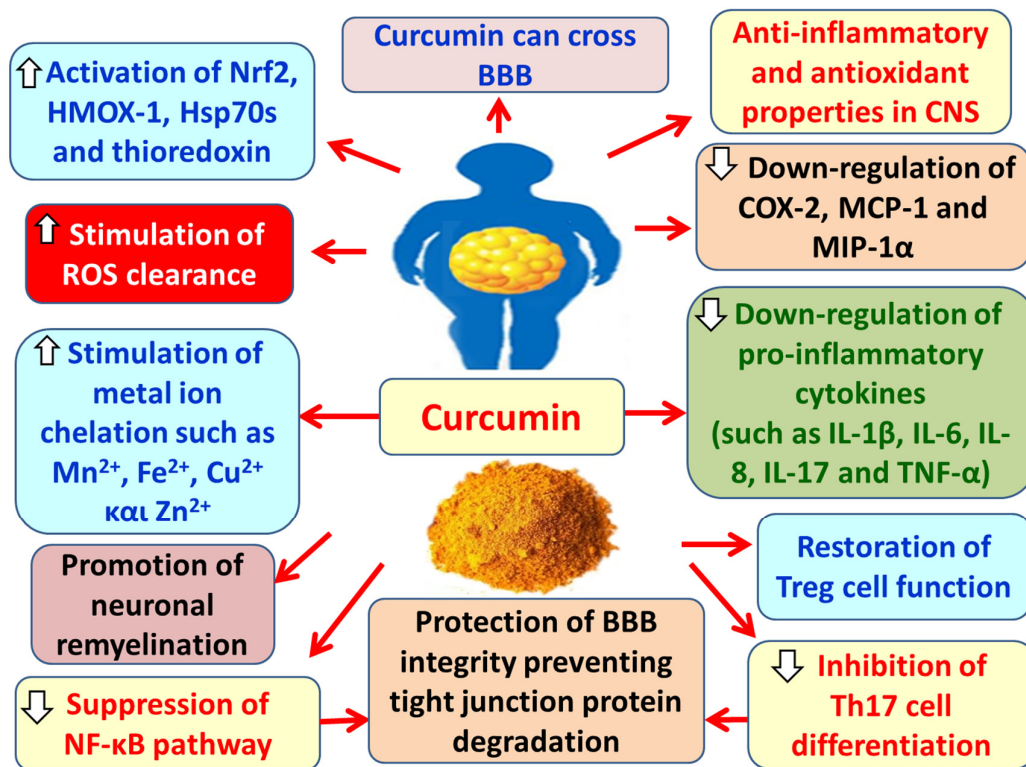

Figure 12. Schematic representation of the beneficial effects of curcumin against MS. Nrf2: nuclear factor erythroid 2-related factor 2; HMOX-1: heme oxygenase 1, Hsp70s: heat shock proteins 70; Mn²⁺: manganous

cation; Fe^{2+}: ferrous cation; Cu^{2+}: copper cation; Zn^{2+}: zinc cation; NF-κB: nuclear factor-κB; CNS: central nervous system; COX-2: cyclooxygenase-2; MCP-1: monocyte chemoattractant protein 1; MIP-1α: macrophage inflammatory protein 1 alpha; IL-1β: interleukin 1β; IL-6: interleukin 6; IL-8: interleukin 8; IL-17; TNF-α: tumor necrosis factor alpha; Th17: T helper 17 cells; BBB: blood-brain barrier.

4.1.4. Resveratrol

Resveratrol enhances the integrity of the BBB, thereby limiting the infiltration of peripheral pro-inflammatory substances and immune cells into the brain parenchyma [227]. It also exerts anti-inflammatory and antioxidant effects in the CNS, reducing reactive oxygen species (ROS) and pro-inflammatory cytokines such as TNF-α, IL-1β, IL-9, IL-12, IL-17, IL-23, and interferon-gamma (IFN-γ) in the CNS [181,225]. Additionally, resveratrol inhibits the expression of MIP-1α [225] and suppresses Th17 helper T cells [228]. At the same time, it promotes the shift of Th1 cells toward Th2 cells, altering cytokine production by T lymphocytes from pro-inflammatory (e.g., TNF-α, IFN-γ, IL-2) to anti-inflammatory (e.g., IL-4, IL-5, IL-10) cytokines [228]. Moreover, resveratrol activates sirtuin 1 (SIRT1), a NAD^+-dependent deacetylase, whose overexpression appears to exert neuroprotective effects [181,228,229]. Resveratrol also enhances remyelination of neurons in experimental autoimmune encephalomyelitis (EAE) models [225]. Due to its anti-inflammatory, antioxidant, and anti-apoptotic properties, it reduces neuronal damage and the severity of MS [225] (Figure 13).
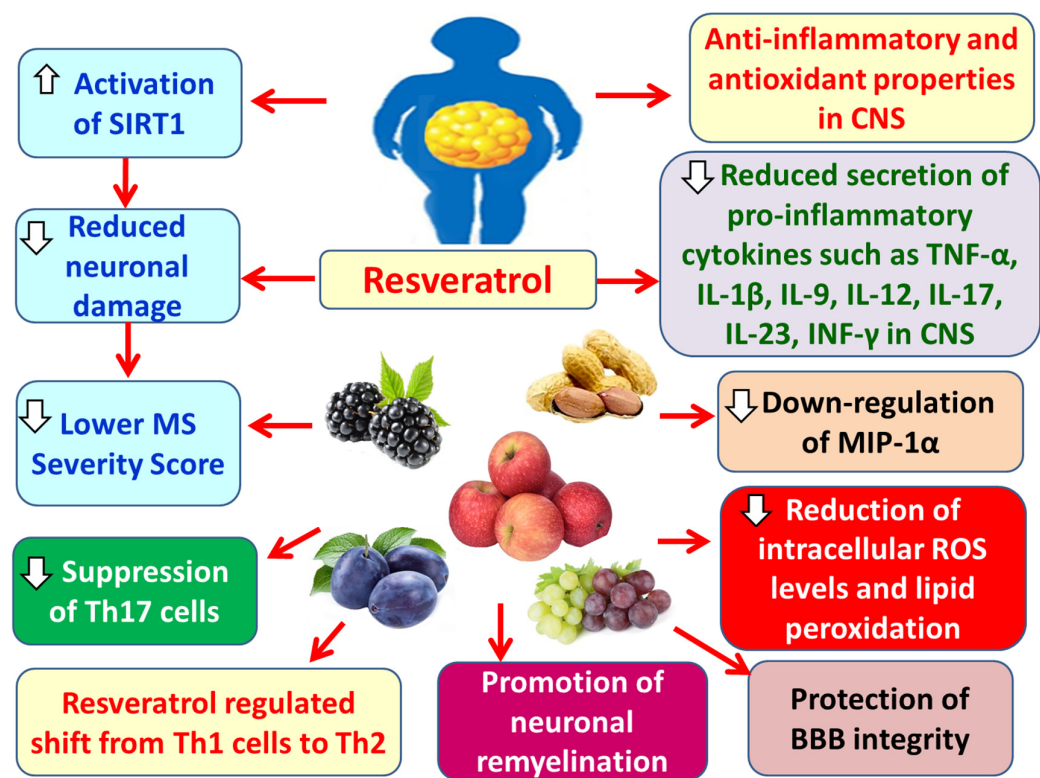

Figure 13. Schematic representation of the beneficial effects of resveratrol against MS. MS: multiple sclerosis; SIRT1: surtuin 1; Th1 cells: T helper 1 cells; Th17 cells: T helper 17 cells; CNS: central nervous system; TNF-α: tumor necrosis factor-alpha; IL-1β: interleukin 1; IL-9: interleukin 9; IL-12: interleukin 12; IL-17: interleukin 17; IL-23: interleukin 23; INF-γ: interferon gamma; ROS: reactive oxygen species; BBB: blood-brain barrier.

4.1.5. Quercetin

Quercetin strengthens the BBB and limits the passage of peripheral pro-inflammatory substances and immune cells into the brain parenchyma [230]. It also demonstrates anti-inflammatory and antioxidant properties in the CNS by promoting ROS clearance, inhibiting the secretion of pro-

inflammatory cytokines such as IL-1β, IL-12, and TNF-α, and chelating metal ions [181,230]. Furthermore, quercetin inhibits nitric oxide synthase activity in cells like macrophages and astrocytes and suppresses the proliferation of autoreactive T cells, which attack the myelin sheath and contribute to the pathogenesis of MS [230]. Similarly, it inhibits the differentiation of Th1 helper T cells [230]. Additionally, quercetin reduces IFN-γ production and inhibits calcium-mediated signaling in CNS cells, exerting neuroprotective effects [181]. It also inhibits xanthine oxidase, an enzyme implicated in axonal and myelin loss in EAE models [181]. Simultaneously, quercetin inhibits the phosphorylation of JAK2, tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription 3 (STAT3), thus exhibiting anti-inflammatory and anti-apoptotic effects in the CNS [181] (Figure 14).
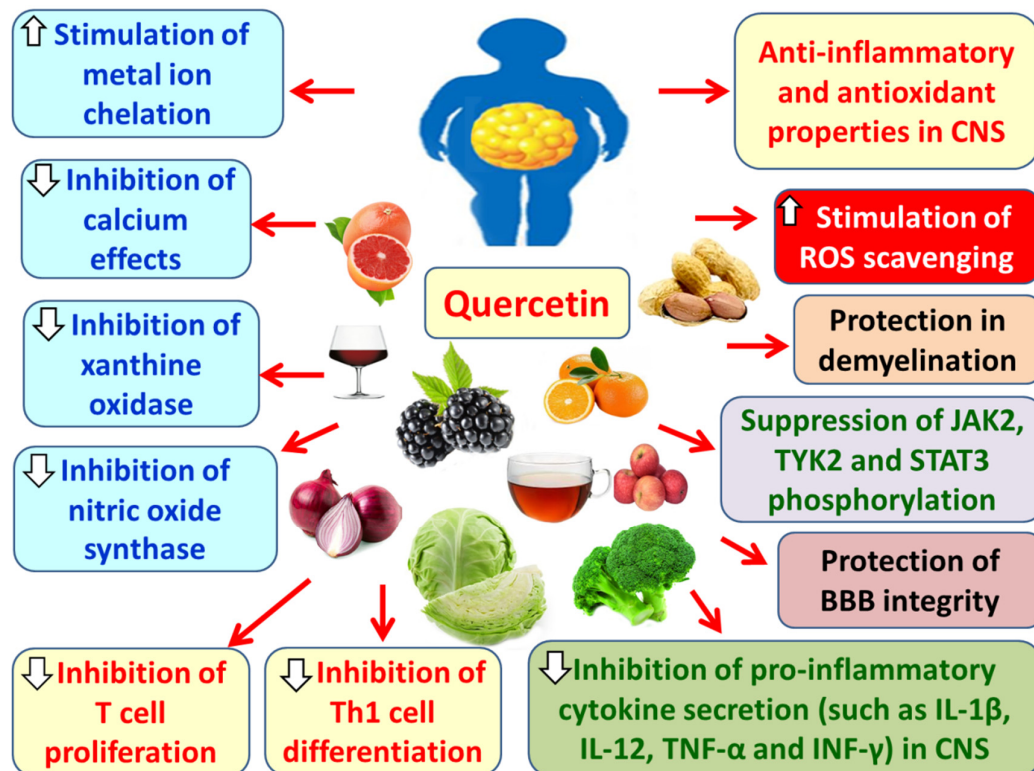

Figure 14. Schematic representation of the beneficial effects of quercetin against MS. MS: multiple sclerosis; Th1 cells: T helper 1 cells; CNS: central nervous system; JKA2: Janus kinase 2; TYK2: tyrosine kinase 2; STAT3: signal transducer and activator of transcription 3; BBB: blood-brain barrier; IL-1β: interleukin 1β; IL-12: interleukin 12, TNF-α: tumor necrosis factor-alpha; INF-γ: interferon gamma.

5. Conclusions

It is now well established that obesity induces neurodegenerative damage in the CNS, due to the chronic inflammation, insulin resistance (IR), and oxidative stress (OS) it causes. In the brains of obese individuals, elevated levels of ROS are produced as a result of persistent neuroinflammation. These high ROS levels act on brain mitochondria, impairing the production of ATP, which is essential for the functioning of neurons and glial cells. Moreover, elevated ROS levels cause damage to the phospholipid membranes of neural cells in the brain. Both chronic neuroinflammation and oxidative stress are involved in the pathophysiology of MS, and the two processes interact with and exacerbate one another. OS results from an imbalance between reactive species and antioxidant systems, favoring oxidative damage. It is also associated with inflammasome signaling, gut microbiota dysbiosis, cytokine-induced synaptic hyperexcitability, abnormal iron accumulation in the brain, and microglial activation, all of which contribute to neuronal injury. Oxidative stress biomarkers

measured in serum or cerebrospinal fluid (CSF) may hold diagnostic and prognostic value, while antioxidant compounds may have potential clinical applications as adjunct therapies in MS. These antioxidant agents appear to exert a positive impact on disease progression, as do innovative therapeutic strategies that target inflammatory mediators by blocking the IL-1 receptor, inhibiting IL-1β or NF-κB, targeting TNF-α, or modulating inflammasomes and activating PPAR pathways. Furthermore, anti-obesity drugs with anti-inflammatory and antioxidant properties may serve as beneficial adjunct treatments for MS. More research is needed to assess the safety and efficacy of new antioxidant compounds as complementary therapies in MS, in two processes, obesity and MS, which, also as this study showed, appear to interact and share common pathophysiological mechanisms.

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