

Review Article

Understanding the Cross-Talk between the Ceramide Biosynthetic Pathway and Mitochondrial Function in Multiple Sclerosis and Demyelinating Disorders

Amarjeet ¹, Raja Babu ¹, Abhipsa Mohapatra,¹ Bhaskaranand Pancholi ¹,
Debapriya Garabadu ¹, Anjali Sharma ², Ashwani Sharma ³ and Md. A. K. Azad ⁴

¹Department of Pharmacology, Central University of Punjab, Bathinda 151401, India

²Freelancer Pharmacovigilance Officer, Uttar Pradesh 201008, India

³School of Pharmaceutical Sciences, MVN University, 121105, Palwal, Haryana, India

⁴Department of Pharmacy, Daffodil International University, Daffodil Smart City, Birulia 1216, Bangladesh

Correspondence should be addressed to Md. A. K. Azad; azad.ph@diu.edu.bd

Received 15 March 2023; Revised 4 September 2023; Accepted 27 September 2023; Published 12 October 2023

Academic Editor: Senthilkumar Subramanian

Copyright © 2023 Amarjeet et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Myelin is a spiral compilation of uniformly thick membranes around the axon in an alternating fashion, and it is formed by a complicated process known as myelination. Myelin sheaths are responsible for various physiological functions such as metabolism, rapid nerve conduction, and maintaining ionic and water homeostasis in the brain. Lipid is one of the major components in the myelin, which includes cholesterol, ceramide, and their derivatives, such as galactosylceramide, sulfatide, and gangliosides. Ceramide and its derivatives are synthesised by various ceramide biosynthetic pathways such as de novo, salvage, sphingomyelinase, and recycling of exogenous ceramide. At an appropriate level, ceramide facilitates the development of the nervous system, cell proliferation, autophagy, and apoptosis, which are responsible for normal functioning, but when the level is altered from normal, it results in mitochondrial dysfunction or cell death through autophagy and apoptosis. The ceramide level increases, especially in the mitochondria. Ceramide level increases in response to oxidative stress which is mediated by inflammatory cytokines. Due to mitochondrial dysfunction, an energy-deficient condition is created because of disruption in the electron transport chain, which results in the death of neurons and glial cells, which subsequently cause demyelination and degeneration of axon. Losing myelin while axons remain relatively intact is the characteristic feature of demyelinating diseases. The primary element of demyelinating disorder is damage, malfunction, failure, or death of mitochondria. These disturbances may occur due to direct or indirect interaction of ceramide with mitochondria. There are several risk factors for demyelination, such as viruses, bacteria, fungi, trauma, obesity, vitamin D deficiency, and genetic and environmental factors. Thus, the review is mainly aimed towards the interaction between ceramide and mitochondria during demyelination.

1. Introduction

The process of forming a myelin sheath is called myelination. Myelin is a spiral compilation of uniformly thick membranes around the axon in an alternating fashion of electron-dense and electron-light layers, referred to as the “major dense line” and the “intraproduct line,” respectively [1]. The major dense line forms compact myelin, which is helpful in saltatory impulse propagation as it yields high electrical

resistance but low capacitance [1]. In contrast to the major dense line, the intraproduct line forms noncompact myelin. This region is much more dynamic than the compact region and hence more metabolically active than the compact region [1]. Schwann cells form myelin in the peripheral nervous system (PNS) while oligodendrocytes in the central nervous system (CNS) [2]. A single myelin sheath is formed by each Schwann cell around an axon, whereas up to 30 sheaths (or more) are formed by each oligodendrocyte

around different axons [2]. Different oligodendrocytes sequentially generate myelin sheaths along the same axon [1]. The core components of myelin are lipids, cholesterol, and proteins. The lipid constitutes approximately 70%, which includes galactosphingolipids and certain phospholipids like sphingomyelin. Cholesterol is responsible for forming the assembly of myelin, and the composition of proteins varies between CNS and PNS myelin [2]. Proteolipid protein and myelin basic protein (MBP) are major components of CNS myelin, but MBP is also a major protein of PNS [2]. Myelin is a structure characterised by its extraordinary stability due to its long half-life. Furthermore, its metabolic stability is also high. The half-life of membrane components varies between weeks and many months; for example, in myelin, cholesterol's half-life is greater than 7–8 months [1]. The majority of oligodendrocytes produce 20–60 myelinating processes having a length of $\sim 20\ \mu\text{m}$ – $200\ \mu\text{m}$. Myelination is a complicated series of processes which can be considered as separate steps for better understanding, including (1) proliferation and migration of oligodendrocyte precursor cells (OPCs) in white matter tracts, (2) recognition of target axons and axon–glia signalling, (3) differentiation of OPCs into myelinating oligodendrocytes, (4) membrane outgrowth and axonal wrapping, (5) trafficking of membrane components, (6) myelin compaction, and (7) node formation [1]. Myelin sheath thickness is strictly controlled and highly associated with the axon's diameter it surrounds, expressed in terms of the g ratio (the diameter of axon/total diameter of fibre) [2]. There is an aggregation of voltage-gated sodium channels at the nodes of Ranvier due to myelination [2]. There is compartmentalisation in oligodendrocytes, where myelin components are synthesised and transported to the growing myelin sheath by various mechanisms [1].

When the process of myelin formation gets hampered or there is a loss of myelin sheath, it results in the pathological condition known as a demyelinating disorder. Demyelination refers to the loss of myelin while axons remain relatively intact. It damages myelin sheaths or the loss of cells that form them. The diseases that occur due to this pathophysiological dysfunction are known as demyelinating disorders. The failure of myelin formation is not a demyelinating disease, but it is explained as dysmyelination. MS is a typical demyelinating disease related to the brain. So, in this review, our concern is restricted to MS. In demyelinating disease, loss of myelin is followed by degeneration of the axon. A reverse of this process may also occur, but that is not a condition of demyelinating disorder [3]. There is a high risk of MS in individuals who have suffered neurologic dysfunction at least once and contain antibodies against myelin proteins such as MOG and MBP [4].

In recent times, there is a considerable increase in the number of demyelinating patients around the globe, especially of multiple sclerosis. Since 2013, more than 2.3 million new MS cases have been reported, including patients of all age groups and gender [5]. Moreover, the actual cause of MS is unknown, but there are various factors which may be responsible for MS, and one of them is altered ceramide biosynthetic pathways [6]. The role of ceramide is crucial

in the process of myelination as it is a prominent component of myelin sheath [7]. The ceramide is produced in the CNS with the help of ceramide biosynthetic pathways such as *de novo*, the *sphingomyelinase* (SMase), the *salvage*, and the *exogenous ceramide-recycling* pathway [8]. It has been reported that when there is an alteration in the level of ceramide, it results in various neurological disorders [9]. The altered ceramide level can be optimised by targeting the different enzymes involved in the ceramide biosynthetic pathways [6]. Hence, these pathways could be a potential target in ameliorating MS.

1.1. Physiology of Myelination. It was thought that myelin is merely responsible for saltatory conduction, but now, it is clear that there is much more responsibility to perform as it is involved in metabolic activities operating in neurons. Myelin helps in maintaining the homeostasis of ions and water and is also involved in activity-dependent neuronal signals [10]. Axon initial segment (AIS) is an unmyelinated segment of CNS neurons which lies between the first myelin sheath and axon hillock of the myelinated axons. The generation of action potentials (APs) in the axon initiates at the AIS, which has a high density of voltage-gated Na^+ and voltage-gated K^+ channels. The former voltage-gated ion channels are critical for the excitability of axons and initiation of AP, while the latter one governs excitability, intrinsic firing as well as AP firing, and waveform [11]. Myelin is an insulator of electrical current and reduces axonal capacitance, which alters the conduction properties and reduces the energy required for propagation of AP, as a consequence of which the nerve conduction becomes more efficient and faster in comparison to unmyelinated axons having equal diameter [12, 13]. Ion channel redistribution in the axon occurs concurrently with the development of the myelin sheath. Voltage-gated Na^+ channels (Na_v) are spread uniformly throughout the axon in the premyelinated or nonmyelinated axon, allowing only slow AP propagation. When the myelin sheaths form, Na_v s and K^+ channels are restricted mainly at the nodes of Ranvier; other ion channels can still be found at juxtaparanodes, the myelinated axon subdomain on the opposite side of the paranodal junction. The generation of AP occurs at the nodes because of the pattern of arrangement of ion channels over the myelinated axon, dramatically enhancing the velocity of conduction of AP in an energy-efficient method referred to as saltatory conduction. The velocity of conduction AP along the axon also depends upon the total number and density of ion channels at the nodes. It was found that if the total number of ion channels in the nodes remains constant, the velocity of AP conduction is inversely proportional to the nodal length while directly proportional if the density of the ion channel remains constant, keeping the nodal length variable [14].

The myelination has a critical role in the homeostasis of water in the brain. There are at least 13 mammalian members of aquaporins (AQPs) (AQPs 0–12), which are expressed in a variety of tissues that transport fluids. These all belong to the family of water channel proteins. In the CNS, there is the presence of AQP1, AQP4, and AQP9, which regulate the water level in the brain. Glia expresses

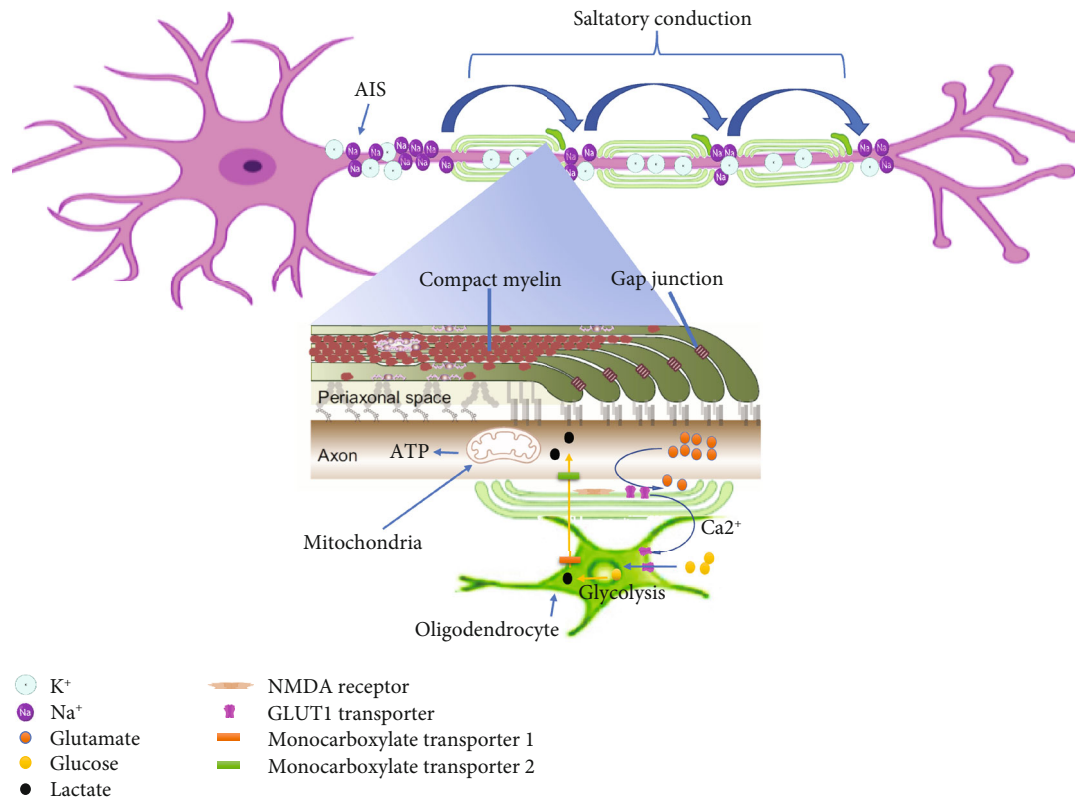


FIGURE 1: The structure and the physiology of myelin sheath.

AQP4, while some neuronal and glial mitochondria contain AQP9. While in PNS, the aquaporin AQP1 is responsible for regulating water, which is present in the myenteric nerve plexuses and submucosal of the oesophagus and in the nerve plexuses of the pancreas. This suggests that there is a differential distribution of AQPs in CNS and PNS [15, 16].

Myelin sheath contains gap junctions responsible for regulating ionic homeostasis and metabolic transport. Gap junctions are made up of connexins. These proteins consist of four transmembrane domains, which are connected with the help of two extracellular loops. The oligomerisation of six connexins forms a hemichannel. Such two hemichannels are placed side by side to form the gap junctions. These junctions are permeable to small molecules and allow the diffusion of ions [10]. The gap junctions may be homotypic (same type of connexins) or heterotypic (different types of connexins) gap junctions. The paranodal region contains homotypic, while the oligodendrocyte/astrocyte contains heterotypic gap junctions. Oligodendrocytes contain connexin (Cx) 32, Cx29, and Cx47, while astrocytes contain Cx30 and Cx43. Cx32 is present in the cell bodies of astrocytes, at the abaxonal membrane, and at the paranodes to form Cx32/Cx32 channels. Cx47/Cx43 and Cx32/Cx30 channels form oligodendrocyte/astrocyte gap junction [17]. The former channel is adjacent to oligodendrocyte somata whereas the latter is at the outer layer of myelin sheaths. The homotypic gap junctions at paranodes are potential sites for modulating paranodal electrical properties during saltatory conduction, while Cx47/Cx43 and Cx32/Cx30 channels

act as conduits for long-distance intracellular and intercellular flows of ions and associated osmotic water. Homotypic and heterotypic oligodendrocyte gap junctions act in series and parallel to provide vital pathways for maintaining intra- and intercellular ionic homeostasis [18]. Any damage or disturbances in the coupling of gap junction may lead to different types of demyelinating disorders such as leukodystrophy and neuromyelitis optica [10]. The structure and the physiology of the myelin sheath are illustrated in Figure 1.

1.2. Role of Ceramide Biosynthetic Pathway in the Physiology of Myelination. Sphingolipids (SLs) are among the top three lipids contributing to membrane formation in eukaryotes. The formation of all SLs takes place from the ceramide. Ceramide is very important because it acts as an intracellular signalling molecule associated with controlling proliferation, differentiation, and cell apoptosis. Sphingosine forms an amide linkage to a fatty acid to yield ceramide. The biosynthetic pathways of ceramide are well documented, and the majority of the relevant enzymes have been recognised and cloned. But more needs to be understood about how ceramide production is controlled under various physiological or pathological circumstances [19, 20].

Ceramide can be produced via different metabolic pathways such as *de novo*, SMase, *salvage*, and the *exogenous ceramide-recycling* pathway [8]. These pathways are well elaborated in Figure 2. Generation of ceramide can be triggered by various factors, including tumour necrosis factor- α (TNF- α), phorbol ester, Fas ligand, heat stress,

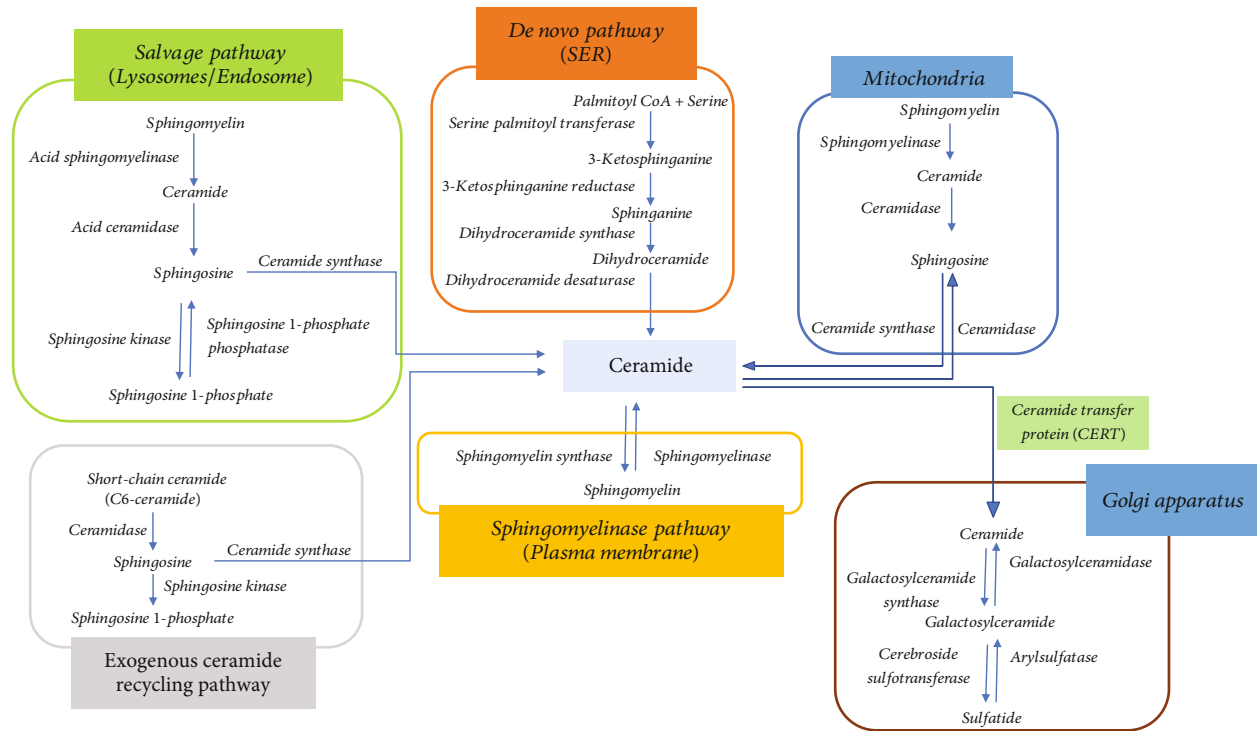


FIGURE 2: Physiology of ceramide synthesis.

chemotherapeutic ionising radiation, cannabinoids, and oxidative stress [21–25].

1.2.1. De Novo Pathway. Endoplasmic reticulum (ER) produces ceramide via a *de novo* pathway that proceeds in the presence of serine palmitoyl transferase enzyme leading to the formation of 3-ketosphinganine after the condensation of L-serine and palmitoyl-CoA. Thereafter, reduction of 3-ketosphinganine to sphinganine takes place via 3-ketosphinganine reductase. This is further followed by dihydroceramide formation after the acylation of sphinganine via dihydroceramide synthase, which is finally reduced to ceramide by dihydroceramide desaturase. Additionally, the metabolism of ceramide produces its complex derivatives, such as cerebroside, in the Golgi apparatus. The ceramide is transported to the Golgi apparatus from the ER by the ceramide transfer protein, CERT, or vesicular trafficking [8, 19].

1.2.2. Salvage Pathway. Ceramide is formed through the breakdown of sphingomyelin via the salvage pathway. During this pathway, sphingomyelin degradation occurs in the acidic environment at the lysosomes or at the late endosomes with the help of the acidic SMase (A-SMase) enzyme to form ceramide. The formed ceramide is further broken down into sphingosine, which permeates into the cytosol and is reversed back to ceramide with the help of the enzyme ceramide synthase [8, 26].

1.2.3. Sphingomyelinase Pathway. This pathway generates ceramide after the hydrolysis of sphingomyelin, which is carried out by neutral SMase isoforms [27]. This pathway

can be reversed back to form sphingomyelin via sphingomyelin synthase enzyme [8].

1.2.4. Exogenous Ceramide-Recycling Pathway. During this pathway, short-chain ceramide (C_6 -ceramide) is converted to sphingosine which is further converted to ceramide [28]. This pathway is catalysed by ceramidase and ceramide synthase, respectively, although some sphingosine is also converted to sphingosine 1-phosphate with the help of the enzyme sphingosine 1-phosphate phosphatase [29].

The involvement of these pathways in demyelinating disorders, especially cuprizone-induced MS, is well documented [6, 30–33]. Ceramide is the central molecule of ceramide biosynthetic pathways, which metabolises into different molecules. The ceramide undergoes phosphorylation in the presence of ceramide kinase to form ceramide-1-phosphate. Both ceramide kinase and ceramide-1-phosphate are involved in regulating several cellular responses. However, it has been reported that inhibition of ceramide kinase could be a potential candidate in the treatment of MS [6]. Further, sphingosine 1-phosphate (S1P), a metabolite of lipid in the ceramide biosynthetic pathways, acts through G-protein-coupled receptors. The agonist of its receptors, such as fingolimod, promotes the survival of oligodendrocytes and remyelination. The S1P is synthesised endogenously with the help of enzyme sphingosine kinase 2 from sphingosine and performs the same task. When there is a deficiency of sphingosine kinase 2, the process of remyelination is blocked, and the level of ceramide and sphingosine remains persistently increased [33].

Moreover, there is an upregulation of the *de novo* pathway rate-limiting enzyme, serine palmitoyltransferase, in

activated astrocytes in the cuprizone-induced MS model of mice. This finding indicates that the ceramide biosynthetic pathways in activated astrocytes may be indirectly responsible for oligodendroglial damage in the brain [32]. Further, it was observed that the inhibition of acid sphingomyelinase by amitriptyline promotes the repair of myelin and provides a novel therapeutic approach for the management of MS [34].

In the last decades, SLs, particularly ceramides, have attracted many researchers' attention, revealing their important role in cellular events and different human neurological disorders. The nervous system is rich in sphingolipids, including ceramide and its derivatives. They comprise a significant portion of the nervous system, mainly as myelin [35]. Ceramide acts as both structural and bioactive molecules that control cellular processes such as the growth of the nervous system, myelination of axon, and upkeep of the stability of myelin. The brain is known to have the second-highest concentration of lipids after adipose tissue, and brain lipids make up 50% of the brain's dry weight [36]. The SL profile of the brain constantly keeps changing as people grow older, proving that SLs are essential for neurodevelopment throughout the lifespan. Alterations in the metabolism of ceramide deeply affect the organisation of the plasma membrane, which alters the myelin ceramide composition which may significantly enhance the risk of demyelination like multiple sclerosis (MS) [37]. Thus, sphingolipids are crucial in developing and maintaining the nervous system and are a significant factor in the emergence of brain diseases.

At the trans-Golgi regions, SMase converts ceramides to sphingomyelin coupled with the synthesis of diacylglycerol, a precursor for glycerol-derived phospholipids crucial in several signalling cascades [38]. Cholesterol and sphingomyelin are highly hydrophobic molecules having a small polar headgroup. Both molecules are intercalated between phospholipid acyl chains and occupy the same spaces. Thus, there is a need for balance between them for the stability of the membrane and signalling function [39].

The naturally occurring ceramides in the myelin membrane are generally long-chain ceramides. Since the long-chain ceramide is highly hydrophobic and nonpolar, it is unable to cross the myelin membrane and remain in the membrane which is essential for the physiological function of myelin [37]. Due to the high order of acyl chain arrangement in the myelin membrane, the fluidity is decreased, and the stability of the membrane is enhanced; thus, tightly packed myelin membrane is formed, which is required for saltatory conduction [9]. Myelin is highly rich in lipids, predominantly sphingolipids and cholesterol. Proper metabolism and their distribution are vital for the growth of the nervous system and the maintenance of physiological processes of the brain. The alteration in their metabolism is commonly related to neurodegenerative diseases [29]. The metabolic products of ceramide, such as galactosylceramide, sulfatide, and gangliosides, play a significant role in the process of myelination. The oligodendrocytes and myelin-forming cells are highly enriched in galactosylceramide and sulfatide. At the same time, the gangliosides are mainly con-

finied to astroglia then in neurons and oligodendrocytes and contribute approximately 5% of brain lipid [9].

In organotypic cultures of the rat cerebellum, ceramide analogues that inhibit or stimulate the cerebrosidease lead to myelination inhibition in the cultures. The potency of the inhibitor analogues in culture is associated with their efficacy in inhibiting cerebrosidease. The ceramide analogue decanoyl amide of 3-phenyl-2-amino-1,3-propanediol with erythroconformation acts as a potent inhibitor. Both groups of analogues distort the myelin sheaths, leading to lipid breakdown into droplets. Although axons are preserved, there are granularity and nuclear changes in neurons. Studies on the potent inhibitor's metabolic effects revealed that glucose transfer to the cerebroside is initially dampened in contrast to proteins and total lipids [40]. Thus, the ceramide analogues inhibit myelination in organotypic culture.

The peripheral surfaces of the compact myelin sheath are exposed by galactosyl ceramides which may confer some beneficial properties to the surface of the myelin membrane, such as the structural integrity of the intact sheath, and help in osmotic and ionic function. The acyl chains of a significant fraction of the lipids in myelin, especially the galactosyl ceramides, are in a crystal form at 37°C if no cholesterol is present. At the hydrophilic/hydrophobic interface of the bilayer, the sugar headgroup and different hydrogen bond donor and acceptor sites in the ceramide portion are engaged in a complex hydrogen bond system. This hydrogen bond system is attributed to the formation of highly compact glycosyl ceramide bilayers and highly compressible phospholipid, cholesterol/glycosyl ceramide systems [41].

Ceramide participates in various metabolic processes, including protein phosphorylation, protein kinase C regulation, and phospholipase A2 modulation, but at high concentrations, it facilitates signal transduction that results in cell death. The ceramide to dihydroceramide ratio in rat brains varies from 4.0 to 4.5 during the usual growth of the brain but is higher in brains affected by MS. In addition to their crucial regulatory roles in myelinogenesis and brain development, they can also directly cause cell death, such as the death of oligodendrocytes in MS [7]. During myelination, sphingosine plays a major role in the synthesis and maturation of oligodendrocytes by activating the melastatin-like transient receptor potential protein 3, facilitating the spontaneous influx of Ca^{2+} [7, 37]. Ceramide is beneficial for the early growth and development of brain cells because it exerts trophic effects at low concentrations and favours cells' survival along their division [42].

1.3. Epidemiology and Etiology Demyelinating Diseases. MS is unevenly distributed worldwide, with high frequency in Europe, North America, Australia, and New Zealand and low frequency in Asia, Africa, and South America [43]. Young adults affected by MS typically belong to the age of 20 and 40 years, while in childhood, onset occurs before 16 years of age in 0.4-10.5% of cases [44].

Lesions in the white matter that progress to form plaques are the defining feature of MS. Mononuclear cells such as lymphocytes, macrophages, and occasionally plasma cells are present in the perivascular of active plaques. The

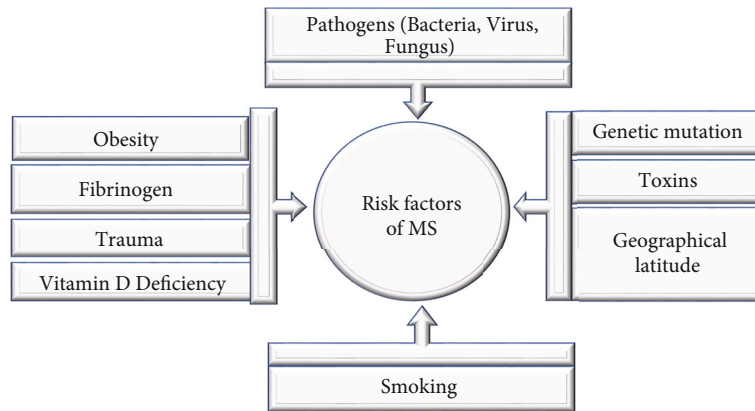


FIGURE 3: Risk factors of multiple sclerosis.

perivascular regions include $CD8^+$ T lymphocytes, while $CD4^+$ T-cells can be seen at the plaque's perimeter. Microglial and astrocytic alterations are frequently seen along with axonal injury and/or loss [45].

The initial damage that occurs in MS is caused by inflammation of tissues of white matter and grey matter in the CNS, brought on by the infiltration of localised immune cells and cytokines associated with them. T helper (Th) cell interference and acquired immune responses, which started by communication between T lymphocytes with antigen-presenting cells (APCs), play important role in the development of MS. Specific cytokines such as interleukin IL-4, IL-12, and IL-23 are produced in response to binding of the pathogen to toll-like receptors (TLRs) present on APCs which stimulate differentiation of $CD4^+$ T-cell into Th1, Th2, or Th17 phenotypes which in turn produce special cytokines such as interferon- γ and tumour necrosis factor- α which are proinflammatory cytokines and ultimately cause inflammation through innate and acquired immunity [46]. MS tissue damage is caused by a complex and dynamic interaction of the immune system with glial cells (oligodendrocytes, astrocytes, and microglia) and neurons. *C. pneumoniae*, a gram-negative bacterium, has been identified to cause MS [47]. MS can be caused by various agents such as the Epstein-Barr virus (EBV) and mononucleosis, fibrinogen, toxins, trauma, low vitamin D, smoking, obesity, and genetic risk factors [48, 49].

Nearly three-quarters of persons with MS are women, but the reason is unknown. Patients with neurologic injury have a higher risk (2–4%) of developing MS than a normal population (0.1%). Also, monozygotic twins are vulnerable to MS. In a genome-wide association study, thousands of samples collected from MS patients and control individuals found that over 200 gene variants can increase the danger of MS. The highly risky among them is the HLA DRB1*1501 haplotype [50, 51]. Most of the risk alleles are associated with the pathway of the autoimmune system. Thus, they may enhance the chances of MS. The environment is a significant factor in the progression of the disease. The primary risk factor is geographical latitude. People residing in temperate climate have a high risk of incidence of MS. It is because of seasonal variation in the exposure to sunlight influencing the level of vitamin D or genetic contribution

[52] along with the prevalence of pathogens in the region. There is ongoing research into how genetic variants and environmental factors increase the chance of acquiring MS.

The risk factor of MS is well illustrated in Figure 3. The mechanisms through which these agents develop MS are explained in Table 1.

1.4. Mitochondrial Dysfunction and Demyelination. The brain requires high energy due to its high metabolic rate. It consumes 20% of all energy produced when the body is at rest. The brain utilises energy mainly for neurotransmission and the axoplasmic flow of impulses. Thus, these functions heavily rely on mitochondrial machinery. Most of this energy passes through the blood-brain barrier and enters the brain as glucose, which is transported by glucose transporters into the brain cells [63].

Several studies revealed that energy imbalance might be a significant factor in the pathophysiology of different neurodegenerative disorders such as MS. Demyelination is the characteristic feature of MS. Both histology techniques and microarray-based gene expression studies identified that there is a mitochondrial failure in MS lesions. Mitochondrial changes in active lesions are defined mainly by a loss of cytochrome C oxidase 1 and a loss of complex IV function in the mitochondrial respiratory chain [64].

During the development of the pathophysiological condition of MS, there are two phases of inflammation: acute and chronic. Initially, there is acute inflammation during a new lesion formation, followed by a chronic inflammatory state, which results in neurodegeneration. Activated immune cells cross the blood-brain barrier (BBB) during acute inflammation and act against the myelin sheath. Inflammation in MS is the result of production and dysregulation of both T lymphocytes (Th1 and Th17) and B-cells of adaptive immune systems. In addition, there is involvement of innate immune systems in inflammation [65, 66]. Mitochondrial dysfunction is a noninflammatory mechanism that may contribute to neurodegeneration in demyelinating disorder [64, 67].

Mitochondria are semiautonomous organelles as they have their DNA apart from nuclear DNA for protein synthesis; that is, mitochondria have dual genomic expression for protein synthesis [68]. The DNA in mitochondria is called mitochondrial DNA (mtDNA), while the other in the

TABLE 1: Mechanism through which different risk factors induce MS.

Sr. no.	Agents	Mechanism	Reference
1	EBV and mononucleosis	Molecular mimicry, B-cell transformation (EBV can transform B-cells through mimicking the receptor signalling; LMP1 mimics CD40 receptor signalling; EBV encodes an interleukin-10-like protein, which is responsible for activates B-cells), and CNS tropism. Further study is needed	[53]
2	Vitamin D deficiency	Suppress lymphocyte stimulation and production, differentiation of T helper cells, and innate immunity while promoting adaptive immunity by releasing inflammatory cytokines mediated by Th1	[54]
3	Trauma	Meta-analyses of case-control studies provide a correlation between trauma of the head and MS incidence, but the mechanism is unknown	[55]
4	Smoking	Tobacco contains intracellular epitopes, modified epitopes, and damage-associated molecular patterns that activate TLRs on alveolar macrophages. In genetically sensitive people, epitopes cross-react with myelin antigens via molecular mimicry. Proinflammatory cytokines released by T lymphocytes act on endothelial cells and compromise the BBB resulting in oxidative stress, inflammation, and microglial activation, all harm myelin and axons	[56]
5	Obesity	Adults and children with a high body fat mass have a deficiency of vitamin D metabolites in their blood. Vitamin D deficiency is connected with an increased risk of MS. It is yet unknown whether greater weight leads towards the high chance of MS incidence solely through vitamin D deficiency or some other mechanism	[57]
6	Fibrinogen	Fibrinogen plays a role in neuroinflammatory responses, implying that it may impact microglia activation, BBB rupture, and axonal injury and consequently develop demyelinating lesions in MS. Further study is needed	[58]
7	Pathogens	In nonneuronal tissues, fungi secrete toxins that target oligodendrocytes and astrocytes, degrading myelin and causing MS Superantigens, produced by bacteria or viruses, significantly stimulate CD4 ⁺ T immune cells, resulting in the proliferation of cells and proinflammatory cytokine release (IL-2) and interferon	[59]
8	Genetic mutation	HLA-DRB1*1501 and IL7R gene are the strong genetic risk factors for the development of MS. Both genes are associated with the immune system. So, when there is an alteration in them, it may result in autoimmune disorders such as MS. However, the exact mechanism still needs to be determined	[50, 51, 60]
9	Toxin	Treatment with repeated doses of mercury after induction of EAE in mice significantly enhanced neurobehavioral scores and mitochondrial damage via ROS production, mitochondrial hypertrophy, MMP failure, and cytochrome C release	[61]
10	Geographical latitude	In higher latitudes, there is inadequate availability of sunlight which results in lower levels of vitamin D	[62]

nucleus that controls their function is called nuclear DNA. The genome of the mitochondria is smaller than the genome of the nucleus. It is highly compacted and has only polymerase γ as DNA polymerase, devoid of introns [69]. The primary function of mitochondria is to produce energy in the form of ATP via the Krebs cycle and oxidative phosphorylation [70, 71]. The mitochondria act upon the electron transport chain (ETC) present on the inner mitochondrial membrane, which is comprised of four complexes (complexes I, II, III, and IV) and complex V or ATP synthase [72]. Additionally, they participate in the sequential reactions of reduction, oxidative phosphorylation, and electron transport through the ETC, which cause the release of energy. The released energy is used to create an electrochemical gradient essential for transporting protons to the inter-

membrane space from the mitochondrial matrix. This gradient is used by ATP synthase to generate ATP [73].

Since mitochondria have multicopy nature of DNA [74], there may be a condition of heteroplasmy (coexistence of wild- and mutated type mtDNA in the same cell) and homoplasmy (presence of only mutated mtDNA in the cell) [75]. There is an increase in mutated mtDNA molecules beyond the threshold at which there is an impairment of the oxidative phosphorylation process [76]. It leads to precipitation and various symptoms of a disease. Mutations in mtDNA occur when there is a lack of histones which protect the mtDNA in a situation with a high level of reactive oxygen species [77]. Mitochondria also play a critical role in neuronal death regulated by the permeability of the outer mitochondrial membrane,

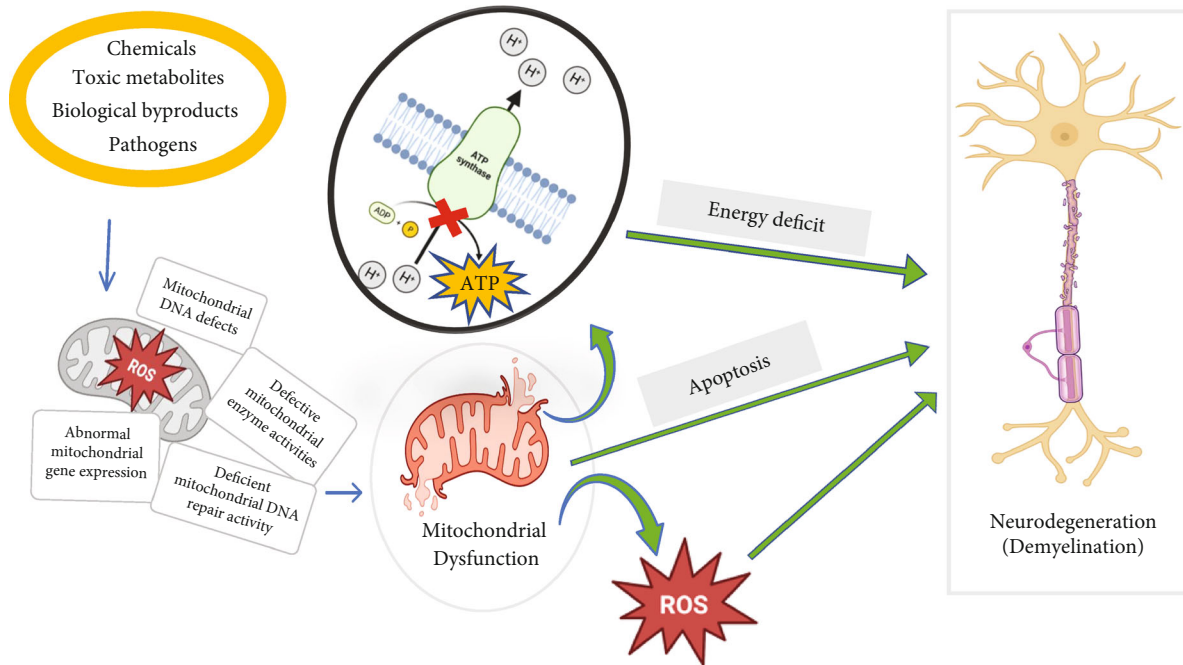


FIGURE 4: Contribution of mitochondrial dysfunction in the demyelination.

which is controlled by several mechanisms. When there is significant permeation in the outer mitochondrial membrane, it leads to the activation of caspases. As a result, there is the release of proapoptotic factors into the cytosol leading to the initiation of the apoptosis cascade. The transmission of the neuronal signal is the result of the propagation of membrane depolarisation across the neuron and the electrochemical gradient generated by the Na^+/K^+ -ATPase, distributed at the nodes. In addition to producing myelin sheaths, oligodendrocytes also provide energy to neurons (release lactate) [78].

The initiation of myelin destruction occurs with chronic inflammation, which leads to the rearrangement of the ion channels. Due to the demyelination, the energy required for the generation of an electrochemical gradient is increased as the number of the Na^+/K^+ -ATPase channels is increased. Consequently, there is a need for more ATP to fulfil the energy demand. To fulfil this requirement, mitochondria start compensatory modifications such as an increase in number and size, delocalisation in the neuron, and their morphology [79, 80].

Parallel to this, chronic inflammation produces a secondary oxidative stress environment apart from ROS release by microglia and macrophages. Additionally, glutamate synthesis rises in response to neuronal injury and the TNF-induced oxidative phosphorylation process via Ca^{2+} -regulated pathways. Due to the progressive mitochondrial damage, there is an alteration in mtDNA and augmentation in heteroplasmy, dysfunction of oxidative phosphorylation subunits, and modification of the proteins that control the organelle's movement from the neuron body to the axon, which subsequently impairs the ATP production and gradient maintenance by the Na^+/K^+ -ATPase after an action potential. As a result, neuronal transmission is impaired,

and accumulation of Na^+ takes place in the neuronal cytoplasm. Due to Na^+ ion accumulation, the $\text{Na}^+/\text{Ca}^{2+}$ channel is forced to transfer Ca^{2+} inside the cell, which activates the Ca^{2+} apoptosis-depend-cascade which subsequently causes the death of neuron, Wallerian degeneration, and irreversible neurological dysfunction [78, 81–83]. The mitochondrial permeability transition pore (PTP) comprises the adenine nucleotide translocator and cyclophilin D present within the mitochondrial matrix. CyPD is an important PTP regulator necessary for triggering Ca^{2+} and oxidative stress-induced cell death [84–86]. The neuron body, dendrites, and pre- and postsynaptic neurons are all affected by the progressive degeneration that starts in the axon. The mitochondrial damage is increased to a greater extent due to the oxidative stress produced by chronic failure to deliver energy to the tissue. In addition, mtDNA damage and change in the levels of heteroplasmy amplify the mitochondrial damage, and the energy supply chain is disrupted, leading to the cell's death [78]. Thus, myelin damage associated with mitochondrial dysfunction is triggered by various mechanisms such as failure to produce energy, apoptosis (mitochondrial injury can elicit proapoptotic events via liberation of apoptosis-induced factor or cytochrome C), and enhanced production of reactive oxygen species [64, 87]. The involvement of mitochondrial dysfunction in the demyelination is shown in Figure 4.

Mitochondrial dysfunction that causes demyelination can occur due to (1) defects in the DNA of mitochondria, (2) abnormal expression of mitochondrial genes, (3) defective activities of mitochondrial enzymes, and (4) deficiency in the repair activity of mitochondrial DNA.

There is significant evidence that demyelination may be exacerbated by mitochondrial disruption. Ultrastructural examination of demyelinated lesions of the spinal cord

revealed a significant reduction in the number of mitochondria and microtubules as well as Ca^{2+} -mediated axonal swelling and death of chronically demyelinated axons.

Recently, it has been explored the association between altered CNS mitochondrial energy metabolism and the development of MS by assessing concentrations of sorbitol, fructose, and lactate in cerebrospinal fluid from people with secondary progressive (SP) MS and relapsing-remitting (RR) MS and healthy controls and concluded that the extramitochondrial glucose metabolism is increased in MS patients and is related with disease progression proved by increasing the Expanded Disability Status Scale score (an indicator of neurological impairment in patients of MS). Thus, CSF metabolic profiling may be beneficial in identifying and monitoring disease progression and aim to maintain or improve mitochondrial glucose metabolism [88].

ROS are produced during biological metabolism as a by-product. The alteration amid cellular ROS generation and the ability of cells to protect against them is called oxidative stress. ROS can oxidise key components of cells like proteins, lipids, and DNA, exclusively the DNA of mitochondria. Oxidative stress induces cellular damage and consequently leads to the death of the cell. There is evidence that oxidative stress plays a primary role in neuronal death in neurodegenerative and neuroinflammatory disorders [89, 90].

Pesticides are used to increase agricultural productivity, but their exposure and residues in plants may increase the risk of developing demyelinating disorders such as MS in both workers and consumers. They cause oxidative stress leading to mitochondrial dysfunctions, which may result in demyelinating disorders. Only some studies provide some insight into the association between pesticide exposure in the environment and MS disease incidence. Organophosphorus pesticides (OPs) are well known for their neurotoxicity due to the permanent suppression of acetylcholinesterase (AChE). These pesticides are the most common causes of contamination for humans. Exposure to OPs leads to an increase in the release of proinflammatory mediators and a decrease in the release of anti-inflammatory cytokines. Additionally, OPs inhibit oxidative phosphorylation and produce a high concentration of ROS, which subsequently leads to mitochondrial dysfunction [91, 92].

1.5. Interaction between Ceramide Biosynthetic Pathway and Mitochondrial Function in Demyelination Diseases. The primary element of demyelinating disorder is the damage, malfunction, failure, or death of mitochondria. These disturbances may occur due to direct or indirect interaction of ceramide with mitochondria. The troubles in mitochondria produce abundant ROS, which causes neuroinflammation, is detrimental to neuronal and glial cells, and ultimately leads to neurodegeneration, including demyelinating disorders [93]. Similarly, failure of mitochondrial function may result from neuroinflammation, which subsequently promotes more rapid damage of neurons and degeneration of myelin. Despite diverse etiological factors, the primary cause for the progressive loss of myelin, i.e., neurodemyelinating disorder, is neuroinflammation and neurodegeneration [94, 95].

The shape of neuronal mitochondria and glucose uptake are considerably changed by cerebrospinal fluid (CSF) in MS patients [96]. Also, mitochondrial complexes I, III, and IV are suppressed, reducing ATP synthesis. These alterations occur in the mitochondria because of the ceramides present in the CSF exosomes and the phosphorylation of dynamin-related protein (DRP) 1. In addition, due to the ceramide-induced mitochondrial metabolic dysfunction, pyruvate uptake decreases, leading to an increase in the extracellular conversion of pyruvate to lactate. This conversion increases lactate levels in CSF. Acute exposure to CSF from patients with MS produces oxidative stress, which attenuates the expression of genes related to neuroprotective action while augmenting the lipid signalling gene expression. Chronic exposure of neuronal and glial cells to stress conditions results in neurotoxicity and failure of bioenergetics after exposure to CSF and is positively associated with the neurofilament light chain concentration. The detrimental actions of CSF on neurons are not because of changes in IgG content, lactate, glucose, or glutamate concentration or variation in the concentration of cytokine, but in the lipidomic profiling, an increase in the concentration of ceramide (C16:0 and C24:0) is identified in the CSF from patients with MS. Neuronal culture exposed to these ceramide species in the form of micelles repeats the same effect that occurs after the exposure of CSF that is oxidative damage and bioenergetic dysfunction. Therefore, C16:0 and C24:0 ceramides are enriched in the CSF of patients with relapsing-remitting MS and are sufficient to induce neuronal mitochondrial dysfunction and axonal damage [81, 97–100]. The potential pathway of neurodegeneration is explored by using a functional screening and live imaging of neuronal mitochondria, which are exposed to the CSF of MS patients, which significantly showed that there is elongation of mitochondria as a significant effect brought on by the CSF. These morphological alterations in mitochondria are correlated with a decrease in the activity of mitochondrial complexes I, III, and IV, as well as with the damage of axons [101]. The unopposed fusion of mitochondria occurs in response to low glucose levels and is caused by the phosphorylation of serine 637 present in the dynamin-related protein DRP1 due to the CSF [102].

There is a differential distribution of ceramide in the CSF of progressive and relapsing-remitting MS patients. It has been documented that the ceramide from the CSF of progressive MS patients induces impairment of mitochondrial respiration and decreases glucose bioavailability in the neurons by enhancing its uptake [103]. This is supported by an *in vitro* study. Neuronal treatment with a ceramide-enriched medium improves the transcripts of specific lactate and glucose transporters, progressively leading to higher glucose absorption from the medium. Interestingly, the inefficient fuel utilisation by the neuronal mitochondria can be countered by supplying lactate or glucose exogenously. Together, these findings point to a “virtual hypoglycemic” condition triggered by the CSF of progressive patients in neuronal culture and point towards a crucial window of opportunity for intervention to reverse the metabolic impairment of neuronal bioenergetics that underlies neurodegeneration in MS patients [97, 104, 105].

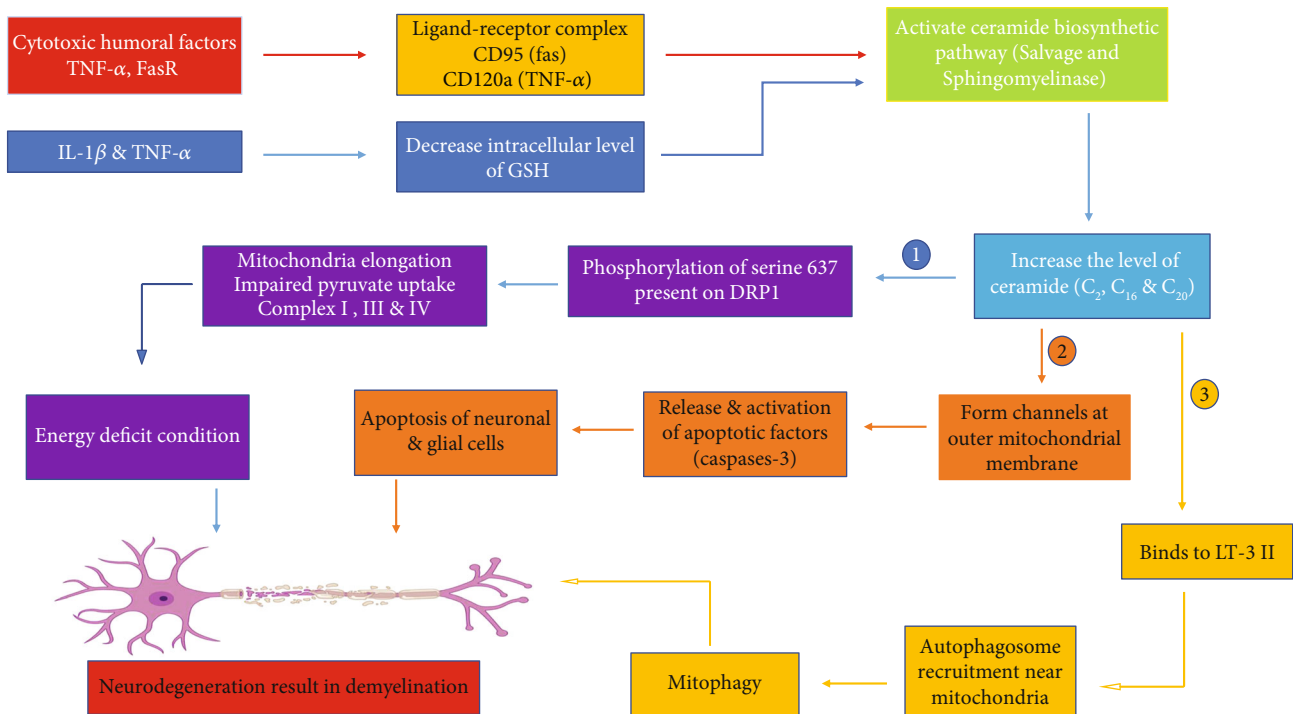


FIGURE 5: Interaction between ceramide biosynthetic pathway and mitochondrial function in demyelination diseases.

The involvement of ceramide in the process of apoptosis has been documented in several studies [106–110]. In early apoptosis, there is augmentation of ceramide levels in cells, especially in mitochondria. This augmented ceramide level triggers cell apoptosis and releases intermembranous space proteins from isolated mitochondria, suggesting that it is proapoptotic. The self-assembly of monomers of ceramide forms large and stable channels that allow the proteins to cross membranes and trigger the apoptotic process [111, 112]. Ceramide, a signalling molecule, accumulates inside cells as a reaction to inflammatory mediators. Ceramide production via the sphingomyelin pathway has been linked to the stimulation of apoptotic cell death in response to cytotoxic humoral agents like Fas ligand (FasL) or tumour necrosis factor- α (TNF- α). Occupancy of either CD95 (Fas-receptor) or CD120a (“type-I” receptor for TNF- α , TNFR1) activates acidic and neutral isoforms of sphingomyelinase which result in more ceramide production within endosomal membranes and plasmalemma, respectively. The proinflammatory effects of TNF- α are facilitated by N-SMase activation, while A-SMase activation promotes the cytokine’s proapoptotic development. Ceramide production is also linked to the potentially fatal consequences of a variety of environmental stimuli, such as thermal shock, ionising radiation, and oxidative stress. This ceramide production is the result of A-SMase activation. In addition, ceramide level is also enhanced by de novo in both neurons and oligodendrocytes [113–115]. In human primary oligodendrocytes, oxidative stress-triggered apoptotic cell death is prevented by antisense suppression of neutral but not acidic sphingomyelinase. Thus, neutral sphingomyelinase could be a potential target for therapeutic intervention in demyelinating disorders such as MS [116, 117].

TNF-alpha or interleukin-1 beta-treated primary astrocytes, microglia, oligodendrocytes, and C6 glial cells of rats resulted in a significant change in cellular redox (reduction in intracellular GSH) and fast breakdown of SM to ceramide. The decline of GSH, increased levels of ceramide, and apoptosis in the brains of human patients with neuroinflammatory diseases indicate that the intracellular GSH level plays a crucial role in the control of cytokine-mediated ceramide generation that results in brain cell apoptosis in these diseases. These effects can be inhibited by the use of antioxidant agents such as N-acetylcysteine and pyrrolidine dithiocarbamate while enhanced by oxidants such as hydrogen peroxide or prooxidants such as aminotriazole [117–121].

Short chains are hydrophilic and soluble, so they cross the membrane without any hindrance [9]. Since C2-ceramide is apoptogenic and short in length, it permeates across the membrane of cells like oligodendroglial cell line MO3.13 and triggers the process of apoptosis, ultimately resulting in cell death. This process is facilitated by the activation of the caspase enzyme. The C2-ceramide activates this enzyme by cleaving pro-caspase-3 and its substrates, fodrin, and gabapentin. Apoptosis of oligodendroglia can be attenuated by inhibiting caspase enzymes using its inhibitor, like BAF. The potential function of caspase-3-like enzymes in the ceramide-induced death of oligodendroglia could have significant effects on how demyelinating disorders are treated [122–124].

Autophagy is crucial in cellular and physiological homeostasis (B. [125]). It permits the recycling of nutrients to the cells obtained from the digestion of organelles at starvation times and the removal of misfolded protein [126]. Autophagy can promote both the survival and death of cells, and both can be triggered by ceramide through various

TABLE 2: Current scenarios for the treatment of MS.

Sr. no.	Therapy	Drug	Mechanisms	Reference
1	Bruton's tyrosine kinase inhibitors (BTKi)	BIO-0556375 (phase 1)	Interaction between B-cells and T-cells is attenuated by BTKi via modulation of metabolic pathways of B-cell. This results in anti-inflammatory modulation and direct inhibition of mitochondrial respiration of B-cell (but not glycolysis)	[137]
		Evobrutinib (phase-II)	Control interaction between B-cell and T-cell during inflammatory CNS demyelination without permanently removing either cell	[138]
2	Myelin repair	Bu Shen Yi Sui	It acts by upregulation of miR-219 or miR-338 expression in exosomes while the expression of their target genes Sox6, Hes5, Sox4, and Lingo1 is inhibited. Further investigation is required to know how exactly the expression of miR-219/338 is increased by BSYSC	[139]
		Clemastine	Used for treatment of demyelination and axonal degeneration in spinal cord injury. Augment oligodendrocyte differentiation and myelination	[140]
3	Immunomodulators	Isosorbide di-(methyl fumarate)	Attenuating oxidative stress through NRF2 stimulation mitigates inflammation and pyroptosis by suppressing NF- κ B and IRF1. Thus, useful in MS treatment	[141]
		Fingolimod	Action is mediated by the modulation of S1P1 on lymphocytes. Significantly enhances the proportion of CD8 ⁺ Treg in MS, reversing the low CD8 ⁺ Treg: CTL (cytolytic T lymphocyte cells) ratio seen in untreated MS	[142, 143]
		Ocrelizumab	It is an anti-CD20 monoclonal antibody that proficiently exhausts B-cells in blood. However, lymphatic organs and an inflammatory CNS have few remaining CD20- plasma and B-cells	[144]
		Interferon β	IFN- β produces its effect mainly by activating the Janus kinase- (JAK-) signal transducers and transcription (STAT) pathway activators	[145]
4	Vaccine	Immunosuppressive biomaterial-based therapeutic vaccine (preclinical)	Immunisation with mesoporous nanoparticles loaded with self-antigen induces Foxp3 ⁺ regulatory T-cell development in the spleen and systemic immunological tolerance in EAE mice, decreasing CNS infiltrating APCs and autoreactive CD4 ⁺ T-cells. Cerium oxide nanoparticles and ROS scavengers exhibit synergistic effects	[146]

pathways. Dysregulation of autophagy has been reported to involve different human diseases, such as cardiovascular diseases, neurodegenerative disorders, and cancer [127]. Lipids such as cardiolipin and ceramide present in the membrane of mitochondria can act as autophagic receptors [128, 129]. Autophagy occurring at a low pace promotes cell survival by removing aggregated protein and damaged organelles which are harmful to the cell [130], but if it occurs with a high intensity for a sustained period, it becomes lethal as there is loss of cellular functions and essential organelles [131]. Excess of ceramide has been found to stimulate lethal mitophagy, which points towards the physiological requirement to limit its concentration at mitochondria. Mitophagy is a selective mitochondrial degradation with the help of the autophagic apparatus. Ceramide has been implicated in the induction of lethal mitophagy. Many studies revealed the capacity of exogenous or endogenous ceramides to trigger the death of cells after their accumulation in the mitochon-

dria. Ceramide directly binds to LC3-II protein, resulting in autophagosome recruitment in the injured mitochondria, causing lethal mitophagy. The process of ceramide-induced mitophagy may occur in oligodendrocyte, astrocyte, and microglial cells [7, 132–136]. Due to the death of mitochondria in these cells, the energy supply chain may get disturbed, and energy-deficient conditions [64] may rise, ultimately leading to the death of these cells and demyelination. More study in this area is necessary to well establish the mechanisms of ceramide-induced mitophagy's role in demyelinating disorders. The interaction between the ceramide biosynthetic pathway and mitochondrial function in demyelination diseases is shown in Figure 5.

1.6. Treatments for MS. There are some therapeutics available for the treatment of MS. The current ongoing therapies are listed in Table 2.

2. Conclusion and Future Perspective

Myelin sheath is an essential structure for the quick and effective transmission of nerve impulses and is also crucial for metabolism in neurons. In the development of myelin sheath, ceramide plays a crucial role. However, if its level increases than normal, it causes demyelination via mitochondrial dysfunction of glial cells and neurons, which may lead to their death. Since ceramide is involved in the pathophysiology of demyelination, the ceramide biosynthetic pathways could be a potential target for the treatment of demyelination. Various enzymes like serine palmitoyl transferase, ceramide synthase, acid sphingomyelinase, and sphingosine kinase, as well as substrates of ceramide biosynthetic pathways, can be targeted to reduce the level of ceramide in diseased conditions. There is a need for further study to find out the mechanism of ceramide-induced mitochondria's role in demyelination.

Abbreviations

AIS:	Axon initial segment
AChE:	Acetylcholinesterase
AP:	Action potential
APCs:	Antigen-presenting cells
A-SMase:	Acid sphingomyelinase
AQPs:	Aquaporins
BBB:	Blood-brain barrier
BTKi:	Bruton's tyrosine kinase inhibitors
CNS:	Central nervous system
COX1:	Cytochrome C oxidase 1
Cx:	Connexin
ETC:	Electron transport chain
MBP:	Myelin basic protein
MS:	Multiple sclerosis
Na _v :	Voltage-gated Na ⁺ channels
OPCs:	Oligodendrocyte precursor cells
OPs:	Organophosphorus pesticides
PNS:	Peripheral nervous system
ROS:	Reactive oxygen species
S1P:	Sphingosine 1-phosphate
SLs:	Sphingolipids
SMase:	Sphingomyelinase
Th:	T helper.

Data Availability

The supporting literature, data, and other necessary information used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] M. Simons and K. A. Nave, "Oligodendrocytes: myelination and axonal support," *Cold Spring Harbor Perspectives in Biology*, vol. 8, no. 1, article a020479, 2015.

[2] J. L. Salzer and B. Zalc, "Myelination," *Current Biology*, vol. 26, no. 20, pp. R971–r975, 2016.

[3] S. Love, "Demyelinating diseases," *Journal of Clinical Pathology*, vol. 59, no. 11, pp. 1151–1159, 2006.

[4] J. Kuhle, C. Pohl, M. Mehling et al., "Lack of association between antimyelin antibodies and progression to multiple sclerosis," *New England Journal of Medicine*, vol. 356, no. 4, pp. 371–378, 2007.

[5] J. A. Gernert, H. Zimmermann, E. Oswald, T. Christmann, T. Kümpfel, and J. Havla, "Clinical onset of CNS demyelinating disease after COVID-19 vaccination: denovo disease?," *Multiple Sclerosis and Related Disorders*, vol. 67, article 104175, 2022.

[6] A. Tanaka, K. Anada, M. Yasue, T. Honda, H. Nakamura, and T. Murayama, "Ceramide kinase knockout ameliorates multiple sclerosis-like behaviors and demyelination in cuprizone-treated mice," *Life Sciences*, vol. 296, article 120446, 2022.

[7] S. Dasgupta and S. K. Ray, "Ceramide and sphingosine regulation of myelinogenesis: targeting serine palmitoyltransferase using microRNA in multiple sclerosis," *International Journal of Molecular Sciences*, vol. 20, no. 20, p. 5031, 2019.

[8] K. Kitatani, J. Idkowiak-Baldys, and Y. A. Hannun, "The sphingolipid salvage pathway in ceramide metabolism and signaling," *Cellular Signalling*, vol. 20, no. 6, pp. 1010–1018, 2008.

[9] C. Mencarelli and P. Martinez-Martinez, "Ceramide function in the brain: when a slight tilt is enough," *Cellular and Molecular Life Sciences: CMLS*, vol. 70, no. 2, pp. 181–203, 2013.

[10] C. Stadelmann, S. Timmler, A. Barrantes-Freer, and M. Simons, "Myelin in the central nervous system: structure, function, and pathology," *Physiological Reviews*, vol. 99, no. 3, pp. 1381–1431, 2019.

[11] A. N. Chand, E. Galliano, R. A. Chesters, and M. S. Grubb, "A distinct subtype of dopaminergic interneuron displays inverted structural plasticity at the axon initial segment," *The Journal of Neuroscience*, vol. 35, no. 4, pp. 1573–1590, 2015.

[12] J. M. Ritchie, "On the relation between fibre diameter and conduction velocity in myelinated nerve fibres," *Proceedings of the Royal Society of London - Series B: Biological Sciences*, vol. 217, no. 1206, pp. 29–35, 1982.

[13] D. Suminaite, D. A. Lyons, and M. R. Livesey, "Myelinated axon physiology and regulation of neural circuit function," *Glia*, vol. 67, no. 11, pp. 2050–2062, 2019.

[14] I. L. Arancibia-Cárcamo, M. C. Ford, L. Cossell, K. Ishida, K. Tohyama, and D. Attwell, "Node of Ranvier length as a potential regulator of myelinated axon conduction speed," *Elife*, vol. 6, article e23329, 2017.

[15] H. Gao, C. He, X. Fang et al., "Localization of aquaporin-1 water channel in glial cells of the human peripheral nervous system," *Glia*, vol. 53, no. 7, pp. 783–787, 2006.

[16] S. D. Shields, J. Mazario, K. Skinner, and A. I. Basbaum, "Anatomical and functional analysis of aquaporin 1, a water channel in primary afferent neurons," *Pain*, vol. 131, no. 1, pp. 8–20, 2007.

[17] C. K. Abrams and S. S. Scherer, "Gap junctions in inherited human disorders of the central nervous system," *Biochimica et Biophysica Acta*, vol. 1818, no. 8, pp. 2030–2047, 2012.

[18] N. Kamasawa, A. Sik, M. Morita et al., "Connexin-47 and connexin-32 in gap junctions of oligodendrocyte somata, myelin sheaths, paranodal loops and Schmidt-Lanterman

- incisures: implications for ionic homeostasis and potassium siphoning," *Neuroscience*, vol. 136, no. 1, pp. 65–86, 2005.
- [19] M. Levy and A. H. Futerman, "Mammalian ceramide synthases," *IUBMB Life*, vol. 62, no. 5, pp. 347–356, 2010.
- [20] M. A. Nyonda, J. Kloehn, P. Sosnowski et al., "Ceramide biosynthesis is critical for establishment of the intracellular niche of *Toxoplasma gondii*," *Cell Reports*, vol. 40, no. 7, article 111224, 2022.
- [21] R. Bose, M. Verheij, A. Haimovitz-Friedman, K. Scotto, Z. Fuks, and R. Kolesnick, "Ceramide synthase mediates daunorubicin-induced apoptosis: an alternative mechanism for generating death signals," *Cell*, vol. 82, no. 3, pp. 405–414, 1995.
- [22] M. Garzotto, M. White-Jones, Y. Jiang et al., "12-O-tetradecanoylphorbol-13-acetate-induced apoptosis in LNCaP cells is mediated through ceramide synthase," *Cancer Research*, vol. 58, no. 10, pp. 2260–2264, 1998.
- [23] G. M. Jenkins, L. A. Cowart, P. Signorelli, B. J. Pettus, C. E. Chalfant, and Y. A. Hannun, "Acute activation of de novo sphingolipid biosynthesis upon heat shock causes an accumulation of ceramide and subsequent dephosphorylation of SR proteins," *The Journal of Biological Chemistry*, vol. 277, no. 45, pp. 42572–42578, 2002.
- [24] S. Schütze, K. Potthoff, T. Machleidt, D. Berkovic, K. Wiegmann, and M. Krönke, "TNF activates NF- κ B by phosphatidylcholine-specific phospholipase C-induced "acidic" sphingomyelin breakdown," *Cell*, vol. 71, no. 5, pp. 765–776, 1992.
- [25] M. Shimabukuro, Y. T. Zhou, M. Levi, and R. H. Unger, "Fatty acid-induced beta cell apoptosis: a link between obesity and diabetes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 5, pp. 2498–2502, 1998.
- [26] B. T. Bikman and S. A. Summers, "Ceramides as modulators of cellular and whole-body metabolism," *The Journal of Clinical Investigation*, vol. 121, no. 11, pp. 4222–4230, 2011.
- [27] L. A. Peña, Z. Fuks, and R. Kolesnick, "Stress-induced apoptosis and the sphingomyelin pathway," *Biochemical Pharmacology*, vol. 53, no. 5, pp. 615–621, 1997.
- [28] V. Chigorno, C. Giannotta, E. Ottico et al., "Sphingolipid uptake by cultured cells: complex aggregates of cell sphingolipids with serum proteins and lipoproteins are rapidly catabolized," *The Journal of Biological Chemistry*, vol. 280, no. 4, pp. 2668–2675, 2005.
- [29] T. Ariga, W. D. Jarvis, and R. K. Yu, "Role of sphingolipid-mediated cell death in neurodegenerative diseases," *Journal of Lipid Research*, vol. 39, no. 1, pp. 1–16, 1998.
- [30] J. L. Dupree, J. L. Mason, J. R. Marcus et al., "Oligodendrocytes assist in the maintenance of sodium channel clusters independent of the myelin sheath," *Neuron Glia Biology*, vol. 1, no. 3, pp. 179–192, 2004.
- [31] H. Jurevics, J. Hostettler, E. D. Muse et al., "Cerebroside synthesis as a measure of the rate of remyelination following cuprizone-induced demyelination in brain," *Journal of Neurochemistry*, vol. 77, no. 4, pp. 1067–1076, 2001.
- [32] S. Kim, A. J. Steelman, Y. Zhang, H. C. Kinney, and J. Li, "Aberrant upregulation of astroglial ceramide potentiates oligodendrocyte injury," *Brain Pathology*, vol. 22, no. 1, pp. 41–57, 2012.
- [33] H. Song, H. P. McEwen, T. Duncan, J. Y. Lee, J. D. Teo, and A. S. Don, "Sphingosine kinase 2 is essential for remyelination following cuprizone intoxication," *Glia*, vol. 69, no. 12, pp. 2863–2881, 2021.
- [34] M. Chami, R. Halmer, L. Schnoeder et al., "Acid sphingomyelinase deficiency enhances myelin repair after acute and chronic demyelination," *PLoS One*, vol. 12, no. 6, article e0178622, 2017.
- [35] D. C. Pant, S. Aguilera-Albesa, and A. Pujol, "Ceramide signalling in inherited and multifactorial brain metabolic diseases," *Neurobiology of Disease*, vol. 143, article 105014, 2020.
- [36] R. E. Cannon, J. C. Peart, B. T. Hawkins, C. R. Campos, and D. S. Miller, "Targeting blood-brain barrier sphingolipid signaling reduces basal P-glycoprotein activity and improves drug delivery to the brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 39, pp. 15930–15935, 2012.
- [37] P. Giussani, A. Prinetti, and C. Tringali, "The role of sphingolipids in myelination and myelin stability and their involvement in childhood and adult demyelinating disorders," *Journal of Neurochemistry*, vol. 156, no. 4, pp. 403–414, 2021.
- [38] K. Hanada, "Serine palmitoyltransferase, a key enzyme of sphingolipid metabolism," *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, vol. 1632, no. 1, pp. 16–30, 2003.
- [39] O. Bakht and E. London, "Cholesterol precursors stabilize ordinary and ceramide-rich ordered lipid domains (lipid rafts) to different degrees. Implications for the Bloch hypothesis and sterol biosynthesis disorders," *Journal of Biological Chemistry*, vol. 281, no. 31, pp. 21903–21913, 2006.
- [40] J. A. Benjamins, J. Fitch, and N. S. Radin, "Effects of ceramide analogs on myelinating organ cultures," *Brain Research*, vol. 102, no. 2, pp. 267–281, 1976.
- [41] C. Lington and M. G. Rumsby, "Galactosyl ceramides of the myelin sheath: thermal studies," *Neurochemistry International*, vol. 3, no. 3–4, pp. 211–218, 1981.
- [42] A. B. Brann, R. Scott, Y. Neuberger et al., "Ceramide signaling downstream of the p75 neurotrophin receptor mediates the effects of nerve growth factor on outgrowth of cultured hippocampal neurons," *The Journal of Neuroscience*, vol. 19, no. 19, pp. 8199–8206, 1999.
- [43] S. S. Soldan and S. Jacobson, "Role of viruses in etiology and pathogenesis of multiple sclerosis," *Advances in Virus Research*, vol. 56, pp. 517–555, 2001.
- [44] C. Renoux, S. Vukusic, Y. Mikaeloff et al., "Natural history of multiple sclerosis with childhood onset," *New England Journal of Medicine*, vol. 356, no. 25, pp. 2603–2613, 2007.
- [45] R. S. Fujinami, M. G. von Herrath, U. Christen, and J. L. Whitton, "Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease," *Clinical Microbiology Reviews*, vol. 19, no. 1, pp. 80–94, 2006.
- [46] N. Ghasemi, S. Razavi, and E. Nikzad, "Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy," *Cell Journal*, vol. 19, no. 1, pp. 1–10, 2017.
- [47] D. H. Gilden, "Infectious causes of multiple sclerosis," *Lancet Neurology*, vol. 4, no. 3, pp. 195–202, 2005.
- [48] A. Ascherio and K. L. Munger, "Epidemiology of multiple sclerosis: from risk factors to prevention—an update," *Seminars in Neurology*, vol. 36, no. 2, pp. 103–114, 2016.
- [49] D. S. Reich, C. F. Lucchinetti, and P. A. Calabresi, "Multiple sclerosis," *New England Journal of Medicine*, vol. 378, no. 2, pp. 169–180, 2018.

- [50] A. Alcina, M. del Mar Abad-Grau, M. Fedetz et al., "Multiple sclerosis risk variant *HLA-DRB1* * 1501 associates with high expression of *DRB1* gene in different human populations," *PLoS One*, vol. 7, no. 1, article e29819, 2012.
- [51] S. G. Gregory, S. Schmidt, P. Seth et al., "Interleukin 7 receptor alpha chain (*IL7R*) shows allelic and functional association with multiple sclerosis," *Nature Genetics*, vol. 39, no. 9, pp. 1083–1091, 2007.
- [52] K. Berer, M. Mues, M. Koutrolos et al., "Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination," *Nature*, vol. 479, no. 7374, pp. 538–541, 2011.
- [53] W. H. Robinson and L. Steinman, "Epstein-Barr virus and multiple sclerosis," *Science*, vol. 375, no. 6578, pp. 264–265, 2022.
- [54] J. Feige, T. Moser, L. Bieler, K. Schwenker, L. Hauer, and J. Sellner, "Vitamin D supplementation in multiple sclerosis: a critical analysis of potentials and threats," *Nutrients*, vol. 12, no. 3, p. 783, 2020.
- [55] L. Harris, S. Hateley, A. Baheerathan, and O. Malik, "A diagnosis of multiple sclerosis following whiplash injury: is there a true association?," *Cureus*, vol. 13, no. 2, article e13411, 2021.
- [56] M. Rosso and T. Chitnis, "Association between cigarette smoking and multiple sclerosis: a review," *JAMA Neurology*, vol. 77, no. 2, pp. 245–253, 2020.
- [57] M. A. Gianfrancesco and L. F. Barcellos, "Obesity and multiple sclerosis susceptibility: a review," *Journal of Neurology & Neuromedicine*, vol. 1, no. 7, pp. 1–5, 2016.
- [58] J. Miranda Acuña, M. Hidalgo de la Cruz, A. L. Ros, S. P. Tapia, M. L. Martínez Ginés, and C. D. de Andrés Frutos, "Elevated plasma fibrinogen levels in multiple sclerosis patients during relapse," *Multiple Sclerosis and Related Disorders*, vol. 18, pp. 157–160, 2017.
- [59] J. E. Libbey, M. F. Cusick, and R. S. Fujinami, "Role of pathogens in multiple sclerosis," *International Reviews of Immunology*, vol. 33, no. 4, pp. 266–283, 2014.
- [60] F. Lundmark, K. Duvefelt, E. Iacobaeus et al., "Variation in interleukin 7 receptor alpha chain (*IL7R*) influences risk of multiple sclerosis," *Nature Genetics*, vol. 39, no. 9, pp. 1108–1113, 2007.
- [61] F. Kahrizi, A. Salimi, F. Noorbakhsh et al., "Repeated administration of mercury intensifies brain damage in multiple sclerosis through mitochondrial dysfunction," *Iranian Journal of Pharmaceutical Research*, vol. 15, no. 4, pp. 834–841, 2016.
- [62] I. P. Carlyle, "Multiple sclerosis: a geographical hypothesis," *Medical Hypotheses*, vol. 49, no. 6, pp. 477–486, 1997.
- [63] N. Meyer and J. E. Rinholm, "Mitochondria in myelinating oligodendrocytes: slow and out of breath?," *Metabolites*, vol. 11, no. 6, p. 359, 2021.
- [64] D. H. Lee, R. Gold, and R. A. Linker, "Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters," *International Journal of Molecular Sciences*, vol. 13, no. 12, pp. 11783–11803, 2012.
- [65] R. Gold, C. Lington, and H. Lassmann, "Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research," *Brain*, vol. 129, no. 8, pp. 1953–1971, 2006.
- [66] T. Korn, "Pathophysiology of multiple sclerosis," *Journal of Neurology*, vol. 255, Supplement 6, pp. 2–6, 2008.
- [67] A. Sharma, T. Singh, D. Pathak, T. Virmani, G. Kumar, and A. Alhalmi, "Antidepressive-like effect of *Aegle marmelos* leaf extract in chronic unpredictable mild stress-induced depression-like behaviour in rats," *BioMed Research International*, vol. 2022, Article ID 6479953, 16 pages, 2022.
- [68] Q. Long, Y. Zhou, H. Wu et al., "Phase separation drives the self-assembly of mitochondrial nucleoids for transcriptional modulation," *Nature Structural & Molecular Biology*, vol. 28, no. 11, pp. 900–908, 2021.
- [69] W. C. Copeland, "The mitochondrial DNA polymerase in health and disease," *Sub-Cellular Biochemistry*, vol. 50, pp. 211–222, 2010.
- [70] A. R. Fernie, F. Carrari, and L. J. Sweetlove, "Respiratory metabolism: glycolysis, the TCA cycle and mitochondrial electron transport," *Current Opinion in Plant Biology*, vol. 7, no. 3, pp. 254–261, 2004.
- [71] I. Martínez-Reyes and N. S. Chandel, "Mitochondrial TCA cycle metabolites control physiology and disease," *Nature Communications*, vol. 11, no. 1, p. 102, 2020.
- [72] J. S. Sousa, E. D'Imprima, and J. Vonck, "Mitochondrial respiratory chain complexes," *Sub-Cellular Biochemistry*, vol. 87, pp. 167–227, 2018.
- [73] E. Fernandez-Vizarra and M. Zeviani, "Mitochondrial disorders of the OXPHOS system," *FEBS Letters*, vol. 595, no. 8, pp. 1062–1106, 2021.
- [74] V. Carelli, A. Maresca, L. Caporali, S. Trifunov, C. Zanna, and M. Rugolo, "Mitochondria: biogenesis and mitophagy balance in segregation and clonal expansion of mitochondrial DNA mutations," *The International Journal of Biochemistry & Cell Biology*, vol. 63, pp. 21–24, 2015.
- [75] Q. Yang, P. Liu, N. S. Anderson et al., "LONP-1 and ATFS-1 sustain deleterious heteroplasmy by promoting mtDNA replication in dysfunctional mitochondria," *Nature Cell Biology*, vol. 24, no. 2, pp. 181–193, 2022.
- [76] I. O. Mazunin, N. V. Volod'ko, E. B. Starikovskaia, and R. I. Sukernik, "Mitochondrial genome and human mitochondrial diseases," *Molekuliarnaia Biologiia*, vol. 44, no. 5, pp. 665–681, 2010.
- [77] D. C. Wallace, W. Fan, and V. Procaccio, "Mitochondrial energetics and therapeutics," *Annual Review of Pathology*, vol. 5, no. 1, pp. 297–348, 2010.
- [78] I. P. Barcelos, R. M. Troxell, and J. S. Graves, "Mitochondrial dysfunction and multiple sclerosis," *Biology*, vol. 8, no. 2, 2019.
- [79] D. Mahad, H. Lassmann, and D. Turnbull, "Review: Mitochondria and disease progression in multiple sclerosis," *Neuropathology and Applied Neurobiology*, vol. 34, no. 6, pp. 577–589, 2008.
- [80] D. J. Mahad, I. Ziabreva, G. Campbell et al., "Mitochondrial changes within axons in multiple sclerosis," *Brain*, vol. 132, no. 5, pp. 1161–1174, 2009.
- [81] R. Dutta, J. McDonough, X. Yin et al., "Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients," *Annals of Neurology*, vol. 59, no. 3, pp. 478–489, 2006.
- [82] T. Dziedzic, I. Metz, T. Dallenga et al., "Wallerian degeneration: a major component of early axonal pathology in multiple sclerosis," *Brain Pathology*, vol. 20, no. 5, pp. 976–985, 2010.

- [83] F. Lu, M. Selak, J. O'Connor et al., "Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis," *Journal of the Neurological Sciences*, vol. 177, no. 2, pp. 95–103, 2000.
- [84] C. P. Baines, R. A. Kaiser, N. H. Purcell et al., "Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death," *Nature*, vol. 434, no. 7033, pp. 658–662, 2005.
- [85] P. Mao and P. H. Reddy, "Is multiple sclerosis a mitochondrial disease?," *Biochimica et Biophysica Acta*, vol. 1802, no. 1, pp. 66–79, 2010.
- [86] T. Nakagawa, S. Shimizu, T. Watanabe et al., "Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death," *Nature*, vol. 434, no. 7033, pp. 652–658, 2005.
- [87] A. Bharadwaj, A. Sharma, T. Singh et al., "Attenuation of strychnine-induced epilepsy employing *Amaranthus viridis* L. leaves extract in experimental rats," *Behavioural Neurology*, vol. 2023, Article ID 6684781, 10 pages, 2023.
- [88] W. T. Regenold, P. Phatak, M. J. Makley, R. D. Stone, and M. A. Kling, "Cerebrospinal fluid evidence of increased extra-mitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression," *Journal of the Neurological Sciences*, vol. 275, no. 1-2, pp. 106–112, 2008.
- [89] L. M. Sayre, G. Perry, and M. A. Smith, "Oxidative stress and neurotoxicity," *Chemical Research in Toxicology*, vol. 21, no. 1, pp. 172–188, 2008.
- [90] M. Valko, D. Leibfritz, J. Moncol, M. T. Cronin, M. Mazur, and J. Telser, "Free radicals and antioxidants in normal physiological functions and human disease," *The International Journal of Biochemistry & Cell Biology*, vol. 39, no. 1, pp. 44–84, 2007.
- [91] E. Costantini, E. Masciarelli, L. Casorri, M. Di Luigi, and M. Reale, "Medicinal herbs and multiple sclerosis: overview on the hard balance between new therapeutic strategy and occupational health risk," *Frontiers in Cellular Neuroscience*, vol. 16, article 985943, 2022.
- [92] T. Galloway and R. Handy, "Immunotoxicity of organophosphorous pesticides," *Ecotoxicology*, vol. 12, no. 1-4, pp. 345–363, 2003.
- [93] A. Mirshafiey and M. Mohsenzadegan, "Antioxidant therapy in multiple sclerosis," *Immunopharmacology and Immunotoxicology*, vol. 31, no. 1, pp. 13–29, 2009.
- [94] K. S. Carvalho, "Mitochondrial dysfunction in demyelinating diseases," *Seminars in Pediatric Neurology*, vol. 20, no. 3, pp. 194–201, 2013.
- [95] M. E. Witte, D. J. Mahad, H. Lassmann, and J. van Horssen, "Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis," *Trends in Molecular Medicine*, vol. 20, no. 3, pp. 179–187, 2014.
- [96] M. Albanese, S. Zagaglia, D. Landi et al., "Cerebrospinal fluid lactate is associated with multiple sclerosis disease progression," *Journal of Neuroinflammation*, vol. 13, no. 1, p. 36, 2016.
- [97] E. Smirnova, D. L. Shurland, S. N. Ryazantsev, and A. M. van der Bliek, "A human dynamin-related protein controls the distribution of mitochondria," *The Journal of Cell Biology*, vol. 143, no. 2, pp. 351–358, 1998.
- [98] O. G. Vidaurre, J. D. Haines, I. Katz Sand et al., "Cerebrospinal fluid ceramides from patients with multiple sclerosis impair neuronal bioenergetics," *Brain*, vol. 137, no. 8, pp. 2271–2286, 2014.
- [99] D. Wheeler, V. V. Bandaru, P. A. Calabresi, A. Nath, and N. J. Haughey, "A defect of sphingolipid metabolism modifies the properties of normal appearing white matter in multiple sclerosis," *Brain*, vol. 131, no. 11, pp. 3092–3102, 2008.
- [100] B. G. Xiao, G. X. Zhang, C. G. Ma, and H. Link, "The cerebrospinal fluid from patients with multiple sclerosis promotes neuronal and oligodendrocyte damage by delayed production of nitric oxide in vitro," *Journal of the Neurological Sciences*, vol. 142, no. 1-2, pp. 114–120, 1996.
- [101] B. Wang, M. Huang, D. Shang, X. Yan, B. Zhao, and X. Zhang, "Mitochondrial behavior in axon degeneration and regeneration," *Frontiers in Aging Neuroscience*, vol. 13, article 650038, 2021.
- [102] R. Yu, T. Liu, C. Ning et al., "The phosphorylation status of Ser-637 in dynamin-related protein 1 (Drp1) does not determine Drp1 recruitment to mitochondria," *The Journal of Biological Chemistry*, vol. 294, no. 46, pp. 17262–17277, 2019.
- [103] B. Westermann, "Bioenergetic role of mitochondrial fusion and fission," *Biochimica et Biophysica Acta*, vol. 1817, no. 10, pp. 1833–1838, 2012.
- [104] T. Wai and T. Langer, "Mitochondrial dynamics and metabolic regulation," *Trends in Endocrinology and Metabolism*, vol. 27, no. 2, pp. 105–117, 2016.
- [105] M. Wentling, C. Lopez-Gomez, H. J. Park et al., "A metabolic perspective on CSF-mediated neurodegeneration in multiple sclerosis," *Brain*, vol. 142, no. 9, pp. 2756–2774, 2019.
- [106] A. Haimovitz-Friedman, R. N. Kolesnick, and Z. Fuks, "Ceramide signaling in apoptosis," *British Medical Bulletin*, vol. 53, no. 3, pp. 539–553, 1997.
- [107] K. Hofmann and V. M. Dixit, "Ceramide in apoptosis—does it really matter?," *Trends in Biochemical Sciences*, vol. 23, no. 10, pp. 374–377, 1998.
- [108] T. Levade, S. Malagarie-Cazenave, V. Gouazé et al., "Ceramide in apoptosis: a revisited role," *Neurochemical Research*, vol. 27, no. 7-8, pp. 601–607, 2002.
- [109] D. K. Perry, "Ceramide and apoptosis," *Biochemical Society Transactions*, vol. 27, no. 4, pp. 399–404, 1999.
- [110] B. J. Pettus, C. E. Chalfant, and Y. A. Hannun, "Ceramide in apoptosis: an overview and current perspectives," *Biochimica et Biophysica Acta*, vol. 1585, no. 2-3, pp. 114–125, 2002.
- [111] M. Colombini, "Ceramide channels and their role in mitochondria-mediated apoptosis," *Biochimica et Biophysica Acta*, vol. 1797, no. 6-7, pp. 1239–1244, 2010.
- [112] N. Ueda, "Ceramide-induced apoptosis in renal tubular cells: a role of mitochondria and sphingosine-1-phosphate," *International Journal of Molecular Sciences*, vol. 16, no. 12, pp. 5076–5124, 2015.
- [113] J. Qin, E. Berdyshev, J. Goya, V. Natarajan, and G. Dawson, "Neurons and oligodendrocytes recycle sphingosine 1-phosphate to ceramide: significance for apoptosis and multiple sclerosis," *The Journal of Biological Chemistry*, vol. 285, no. 19, pp. 14134–14143, 2010.
- [114] A. A. Shamseddine, M. V. Airola, and Y. A. Hannun, "Roles and regulation of neutral sphingomyelinase-2 in cellular and pathological processes," *Advances in Biological Regulation*, vol. 57, pp. 24–41, 2015.
- [115] W. Stoffel, "Functional analysis of acid and neutral sphingomyelinases in vitro and in vivo," *Chemistry and Physics of Lipids*, vol. 102, no. 1-2, pp. 107–121, 1999.

- [116] A. Jana and K. Pahan, "Oxidative stress kills human primary oligodendrocytes via neutral sphingomyelinase: implications for multiple sclerosis," *Journal of Neuroimmune Pharmacology*, vol. 2, no. 2, pp. 184–193, 2007.
- [117] S. Rossi, C. Motta, V. Studer et al., "Tumor necrosis factor is elevated in progressive multiple sclerosis and causes excitotoxic neurodegeneration," *Multiple Sclerosis*, vol. 20, no. 3, pp. 304–312, 2014.
- [118] B. Liu, N. Andrieu-Abadie, T. Levade, P. Zhang, L. M. Obeid, and Y. A. Hannun, "Glutathione regulation of neutral sphingomyelinase in tumor necrosis factor- α -induced cell death," *The Journal of Biological Chemistry*, vol. 273, no. 18, pp. 11313–11320, 1998.
- [119] B. Liu and Y. A. Hannun, "Inhibition of the neutral magnesium-dependent sphingomyelinase by glutathione," *The Journal of Biological Chemistry*, vol. 272, no. 26, pp. 16281–16287, 1997.
- [120] D. Obradović, M. Kataranovski, E. Dincić, S. Obradović, and M. Colić, "Tumor necrosis factor- α and interleukin-4 in cerebrospinal fluid and plasma in different clinical forms of multiple sclerosis," *Vojnosanitetski Pregled*, vol. 69, no. 2, pp. 151–156, 2012.
- [121] I. Singh, K. Pahan, M. Khan, and A. K. Singh, "Cytokine-mediated induction of ceramide production is redox-sensitive. Implications to proinflammatory cytokine-mediated apoptosis in demyelinating diseases," *The Journal of Biological Chemistry*, vol. 273, no. 32, pp. 20354–20362, 1998.
- [122] K. Akassoglou, J. Bauer, G. Kassiotis et al., "Oligodendrocyte apoptosis and primary demyelination induced by local TNF/ α signaling in the central nervous system of transgenic mice: models for multiple sclerosis with primary oligodendroglialopathy," *The American Journal of Pathology*, vol. 153, no. 3, pp. 801–813, 1998.
- [123] M. Craighead, J. Pole, and C. Waters, "Caspases mediate C2-ceramide-induced apoptosis of the human oligodendroglial cell line, MO3.13," *Neuroscience Letters*, vol. 278, no. 3, pp. 125–128, 2000.
- [124] E. E. Ochu, N. J. Rothwell, and C. M. Waters, "Caspases mediate 6-hydroxydopamine-induced apoptosis but not necrosis in PC12 cells," *Journal of Neurochemistry*, vol. 70, no. 6, pp. 2637–2640, 1998.
- [125] B. Levine and G. Kroemer, "Biological functions of autophagy genes: a disease perspective," *Cell*, vol. 176, no. 1–2, pp. 11–42, 2019.
- [126] K. R. Parzych and D. J. Klionsky, "An overview of autophagy: morphology, mechanism, and regulation," *Antioxidants & Redox Signaling*, vol. 20, no. 3, pp. 460–473, 2014.
- [127] K. H. Kim and M. S. Lee, "Autophagy—a key player in cellular and body metabolism," *Nature Reviews Endocrinology*, vol. 10, no. 6, pp. 322–337, 2014.
- [128] C. T. Chu, H. Bayir, and V. E. Kagan, "LC3 binds externalized cardiolipin on injured mitochondria to signal mitophagy in neurons: implications for Parkinson disease," *Autophagy*, vol. 10, no. 2, pp. 376–378, 2014.
- [129] R. D. Sentelle, C. E. Senkal, W. Jiang et al., "Ceramide targets autophagosomes to mitochondria and induces lethal mitophagy," *Nature Chemical Biology*, vol. 8, no. 10, pp. 831–838, 2012.
- [130] B. Levine and G. Kroemer, "Autophagy in the pathogenesis of disease," *Cell*, vol. 132, no. 1, pp. 27–42, 2008.
- [131] X. Li, S. He, and B. Ma, "Autophagy and autophagy-related proteins in cancer," *Molecular Cancer*, vol. 19, no. 1, p. 12, 2020.
- [132] M. Dany and B. Ogretmen, "Ceramide induced mitophagy and tumor suppression," *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, vol. 1853, no. 10, Part B, pp. 2834–2845, 2015.
- [133] A. Del Grosso, S. Antonini, L. Angella, I. Tonazzini, G. Signore, and M. Cecchini, "Lithium improves cell viability in psychosine-treated MO3.13 human oligodendrocyte cell line via autophagy activation," *Journal of Neuroscience Research*, vol. 94, no. 11, pp. 1246–1260, 2016.
- [134] W. Li, J. Feng, C. Gao et al., "Nitration of Drp1 provokes mitophagy activation mediating neuronal injury in experimental autoimmune encephalomyelitis," *Free Radical Biology & Medicine*, vol. 143, pp. 70–83, 2019.
- [135] S. Patergnani, M. Bonora, S. Ingusci et al., "Antipsychotic drugs counteract autophagy and mitophagy in multiple sclerosis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 118, no. 24, 2021.
- [136] Y. Rui and J. Q. Zheng, "Amyloid β oligomers elicit mitochondrial transport defects and fragmentation in a time-dependent and pathway-specific manner," *Molecular Brain*, vol. 9, no. 1, p. 79, 2016.
- [137] R. Li, H. Tang, J. C. Burns et al., "BTK inhibition limits B-cell-T-cell interaction through modulation of B-cell metabolism: implications for multiple sclerosis therapy," *Acta Neuropathologica*, vol. 143, no. 4, pp. 505–521, 2022.
- [138] S. Torke, R. Pretzsch, D. Häusler et al., "Inhibition of Bruton's tyrosine kinase interferes with pathogenic B-cell development in inflammatory CNS demyelinating disease," *Acta Neuropathologica*, vol. 140, no. 4, pp. 535–548, 2020.
- [139] J. Ji, Y. Q. Sun, Z. Zha et al., "Bu Shen Yi Sui capsules promote remyelination by regulating microRNA-219 and microRNA-338 in exosomes to promote oligodendrocyte precursor cell differentiation," *Evidence-based Complementary and Alternative Medicine*, vol. 2022, Article ID 3341481, 19 pages, 2022.
- [140] W. Du, Y. Deng, R. Jiang, L. Tong, R. Li, and X. Jiang, "Clemastine enhances myelination, delays axonal loss and promotes functional recovery in spinal cord injury," *Neurochemical Research*, vol. 47, no. 2, pp. 503–515, 2022.
- [141] W. R. Swindell, K. Bojanowski, and R. K. Chaudhuri, "Transcriptomic analysis of fumarate compounds identifies unique effects of isosorbide di-(methyl fumarate) on NRF2, NF- κ B and IRF1 pathway genes," *Pharmaceuticals*, vol. 15, no. 4, p. 461, 2022.
- [142] J. Chun and H. P. Hartung, "Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis," *Clinical Neuropharmacology*, vol. 33, no. 2, pp. 91–101, 2010.
- [143] T. W. Houston, Q. Howlett-Prieto, C. Regenauer et al., "Increased percentage of CD8(+)/CD28(-) regulatory T cells with fingolimod therapy in multiple sclerosis," *Neurology-Neuroimmunology Neuroinflammation*, vol. 10, no. 2, article e200075, 2023.
- [144] M. Margoni, P. Preziosa, P. Tortorella, M. Filippi, and M. A. Rocca, "Does ocrelizumab limit multiple sclerosis progression? Current evidence from clinical, MRI, and fluid biomarkers," *Neurotherapeutics*, vol. 19, no. 4, pp. 1216–1228, 2022.

- [145] D. Jakimovski, C. Kolb, M. Ramanathan, R. Zivadinov, and B. Weinstock-Guttman, "Interferon β for multiple sclerosis," *Cold Spring Harbor Perspectives in Medicine*, vol. 8, no. 11, 2018.
- [146] T. L. Nguyen, Y. Choi, J. Im et al., "Immunosuppressive biomaterial-based therapeutic vaccine to treat multiple sclerosis via re-establishing immune tolerance," *Nature Communications*, vol. 13, no. 1, p. 7449, 2022.