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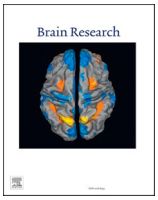

Review

Potential biomaterials and experimental animal models for inventing new drug delivery approaches in the neurodegenerative disorder: Multiple sclerosis

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ABSTRACT

The tight junction of endothelial cells in the central nervous system (CNS) has an ideal characteristic, acting as a biological barrier that can securely regulate the movement of molecules in the brain. Tightly closed astrocyte cell junctions on blood capillaries are the blood–brain barrier (BBB). This biological barrier prohibits the entry of polar drugs, cells, and ions, which protect the brain from harmful toxins. However, delivering any therapeutic agent to the brain in neurodegenerative disorders (i.e., schizophrenia, multiple sclerosis, etc.) is extremely difficult. Active immune responses such as microglia, astrocytes, and lymphocytes cross the BBB and attack the nerve cells, which causes the demyelination of neurons. Therefore, there is a hindrance in transmitting electrical signals properly, resulting in blindness, paralysis, and neuropsychiatric problems. The main objective of this article is to shed light on the performance of biomaterials, which will help researchers to create nanocarriers that can cross the blood–brain barrier and achieve a therapeutic concentration of drugs in the CNS of patients with multiple sclerosis (MS). The present review focuses on the importance of biomaterials with diagnostic and therapeutic efficacy that can help enhance multiple sclerosis therapeutic potential. Currently, the development of MS in animal models is limited by immune responses, which prevent MS induction in healthy animals. Therefore,

Abbreviations: MS, Multiple sclerosis; WM, White matter; CNS, Central nervous system; MRI, Magnetic resonance imaging; BBB, Blood-brain barrier; RRMS, Relapsing-remitting MS; SPMS, Secondary-progressive MS; PPMS, Primary-Progressive MS; PRMS, Progressive-Relapsing MS; OPCs, Oligodendrocyte precursor cells; IFN, Interferon; MHC I and II, Major histocompatibility I and II; TNF, Tumor necrosis factor; IL-1, Interleukin-1; OL, Oligodendrocytes; DHODH, dihydroorotate dehydrogenase; DHO, Dihydroorotate; CPMS, Chronic progressive MS; GA, Glatiramer acetate; MBP, Myelin basic protein; Th2, Helper T cells type II; Tregs, Regulatory T cells; Th17, Helper T cells type 17; NF-kB, Nuclear factor kappa activated B cells; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; OSGIN1, Oxidative Stress-Induced Growth Inhibitor 1; S1P1, Sphingosine-1 phosphate; CD20, Cluster of differentiate 20; PLP, Proteolipid protein; MOG, Myelin oligodendrocyte glycoprotein; EAE, Experimental autoimmune encephalomyelitis; LIF, Leukemia inhibitory factor; ECD, Ethylene dicysteine diethyl ester; EGF, Epidermal growth factor; MAG, Myelin-associated glycoprotein; CNPase, 2′3′-cyclic nucleotide 3′-phosphodiesterase; TMEV, Theiler's murine encephalomyelitis virus; GM, Gray matter; HLA-DR, human leukocyte antigen-DR; NAWM, Normal-appearing white matter; NADPH, Nicotinamide adenine dinucleotide phosphate; TWEAK, TNF-related weak inducer of apoptosis; MSR, Macrophage scavenger receptor; ROS, Reactive oxygen species; MPO, Myeloperoxidase; APOE, Apolipoprotein E; TREM2, Triggering receptor expressed on myeloid cells 2; CSF1R, Colony-stimulating factor 1 receptor; IGF1, Insulin-like growth factor 1; MMPs, matrix metalloproteinases; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; CX3CR1, CX3C motif chemokine receptor 1; TGM2, Transglutaminase 2; CFA, Complete Freund's Adjuvant; TAK1, TGFb-activated kinase 1; NLRP3, Nod-like receptor protein 3; INFg, Interferon-gamma; IL-6R, Interleukin-6 receptors; TGFb, Transforming Growth-Factor-b; AT1R, Angiotensin II type-1 receptor; VEGF-B, Microglial vascular endothelial growth factor B; mDCs, Myeloid dendritic cells; DCs, Dendritic cells; FLT-1, Fms-like Tyrosine Kinase 1 (FLT-1); CCR8, chemokine receptor 8; GM-CSF, Granulocyte-macrophage colony-stimulating factor; TLR, Toll-like receptor; 15-HC, 15-alphahydroxicholestene; iNOS, Inducible nitric oxide synthase; S1P, Sphingosine-1-phosphate; EBV, Epstein-Barr virus; GDVII, George's disease 7; TO, Theiler's original; DA, Daniels; LPC, Lysophosphatidylcholine; Vα and Vβ, Pon-restricted T cell receptor Vα and Vβ; CD8 and CD4 cells, cluster of differentiation 8 and 4 cells; OPC, Oligodendrocyte progenitors; ATP, Adenosine triphosphate; SLNs, Solid lipid nanoparticles; NLCs, Nanostructured lipid carriers; DDS, Drug delivery system; PLGA, Poly(lactic-co-glycolic) acid; miRNA, MicroRNA; NPs, Nanoparticles; GNPs, Gold nanoparticles.

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this article also showcases animal models currently used for treating MS. A future advance in developing a novel effective strategy for treating MS is now a potential area of research.

1. Introduction

Multiple sclerosis (MS) is a white matter (WM) demyelinating disorder of the central nervous system (CNS) (Pirko and Noseworthy, 2007; Zalc, 2018). The researchers such as Carswell, Cruveilhier, Charcot, and others identified the pathological indications of MS 100 years ago (Zalc, 2018). Many unwanted autoimmune responses, like activated lymphocytes, astrocytes, and microglia cells, have responsible for demyelination (Glass et al., 2010; Kocur et al., 2015). The pathological hallmark of MS has chronic neurodegeneration of myelin sheaths, which leads to axonal damage (Ahn et al., 2022; Koutsoudaki et al., 2020). This disruption transpires neuropsychiatric problems and permanent disability in a patient (Diem et al., 2003). Diagnosis in MS depends on the patient's clinical findings and confirmation of support for magnetic resonance imaging (MRI) (Filippi et al., 2016).

MS usually appears in people aged 20–50 years, and women are generally more aggressive in evolving MS (Syed, 2018). MS is an orphan disease that affects around 500,000 individuals only in the USA, and more than 2.8 million people suffer worldwide (Dilokthornsakul et al., 2016). Fig. 1 shows the global prevalence of mortality and the population affected by MS in 2013 and 2020. More than 20,000 patients died due to MS in 2013, with a prevalence rate of 35.9 per 100,000 persons and an incidence rate of 2.1 per 100,000. During 2020, according to the report published by the world health organization, certain areas, such as Europe (45.28 %) and America (37.25 %), will have greater MS prevalence than the global prevalence. Contrarily, the places where the prevalence of MS is lower than that internationally include the Eastern Mediterranean (10.46 %), South-East Asia (2.73 %), Africa (2.75 %), and Western Pacific (1.52 %) (Abuawad et al., 2022; Wallin et al., 2019). Hence, Europe and America have 82.53 % of prevalence than other areas. Consequently, the prevalence rate of MS increased to 7.95 % in America in 2020 than in 2013, but the highest death rate is reported globally in the United Kingdom (Walton et al., 2020).

Present treatments of brain disorders have usually been associated with various limitations, such as the blood–brain barrier (BBB) and many unwanted side effects. (Balasa et al., 2021; E. Konofagou et al., 2012). Many researchers have focused on nanoscale strategies with potential implementation in CNS disorders such as multiple sclerosis, Parkinson's, and Alzheimer's disease, etc., (Díaz-García et al., 2022; El Ouaamari et al., 2023; Mittal et al., 2022). Nanomedicine has enhanced the possible prognosis and brain-targeted therapies in various neurodegenerative disorders (El Ouaamari et al., 2023). Recently, several articles reported that biomaterials are highly selective and applicable for molecular detection, targeted drug delivery, therapeutic monitoring and diagnosis of various neurodegenerative disorders (Díaz-García et al., 2022; Mittal et al., 2022).

Present study has focused on the limitations of conventional therapies, the advancement of biomaterials in treating autoimmune disorders, and the recently used animal models to study MS. That provides a scope into the near future to improve the therapeutic aspects of MS.

2. Multiple sclerosis

The term multiple sclerosis (MS) refers to a wound, lesion, or section that looks like "multiple" pieces of WM in the brain (Hulst and Geurts, 2011; Segal, 2019). The etiology and causes of MS are still unclear. However, hypotheses suggested that heredity and immune infections such as viruses, metabolic factors, uncontrolled immunological factors, or environmental factors combine to cause repeated immune attacks to the myelin sheath in the CNS, leading to MS (Joshua et al., 2022). MS

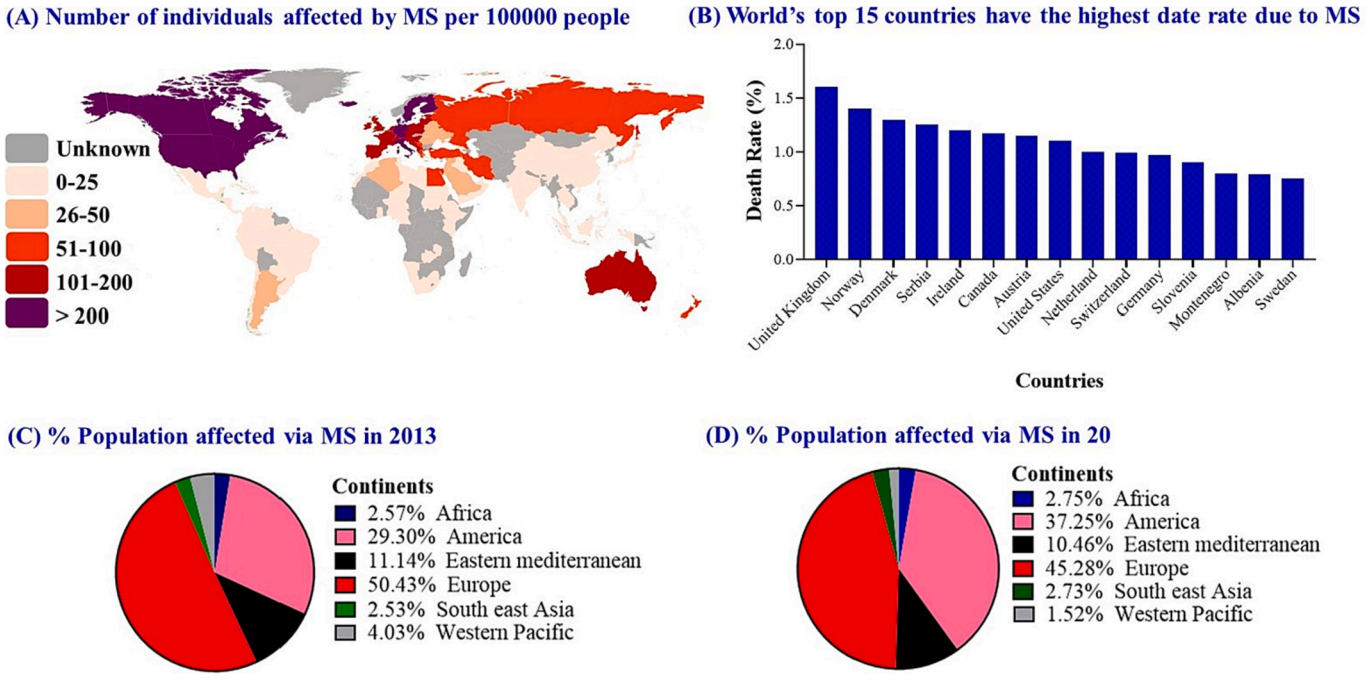

Fig. 1. Global prevalence of MS. **(A)** Map displaying regional differences in MS prevalence and the number of individuals affected by MS per 100,000 people by nation: Grey is used to indicate countries without prevalence statistics or data or with statistics but no source information. According to the key, scores of 0–25, 26–50, 51–100, 101–200, and > 200 individuals affected per 100,000 people are displayed in varying tones of violet, red, orange, peach, and pale peach, respectively. **(B)** World's top 15 countries with the highest death rate due to MS. **(C)** % population affected due to MS in 2013 and **(D)** % population affected via MS in 2020.

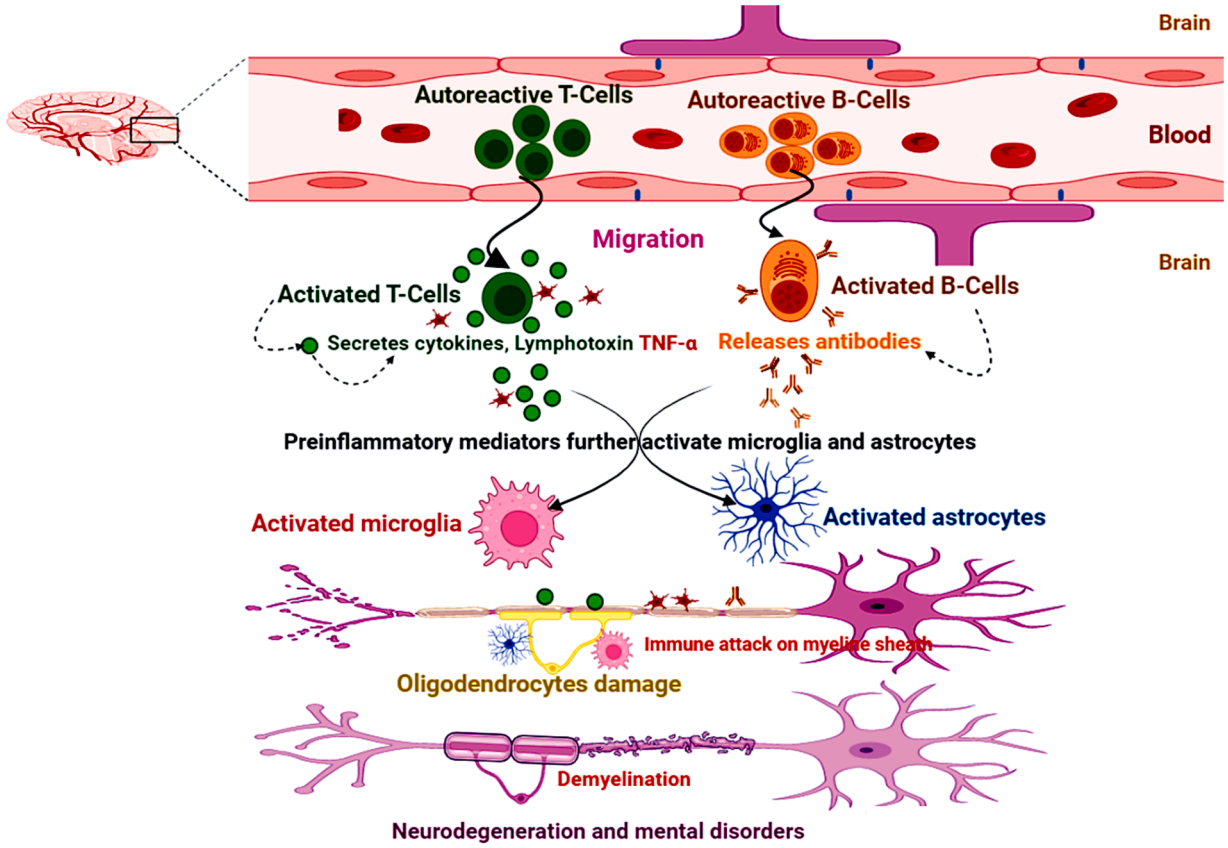

Fig. 2. The mechanism involved in MS progression: In this context, infectious material (neurotoxin, virus, bacteria, or any pathogen) enters blood vessels in the brain, causing stimulation/activation of T and B cells (Dolati et al., 2017). These activated cells further migrate from blood to the brain and secrete many inflammatory mediators (cytokines, lymphotoxins, and TNF-α) that activate microglia and astrocyte cells (Zéphir, 2018). These activated microglia and astrocytes subsequently damage the oligodendrocyte precursor cells (OPCs), amplifying MS demyelination and neurodegeneration (Dutta and Trapp, 2011; Psenicka et al., 2021).

injuries appear in the WM within the neurons, brain stem, ganglia, and spinal cord. WM is an essential part of neurons, which helps transmit signals from the grey matter (Lassmann, 2018). The primary function of WM is to gather information about the whole body. MS is occurred due to unwanted immune responses that directly attack the neurons, leading to demyelination and the formation of lesions in the CNS (Compston and Coles, 2008; Kamma et al., 2022; Melchor et al., 2019). Fig. 2 illustrates the mechanisms involved in MS progression. Neurons are involved in conducting electrical impulses in the human body. Demyelination disrupts electrical impulses, leading to mental problems and paralysis (Girão et al., 2022; Maugeri et al., 2021). As the frequency of recurrence of astrocytes increases, so does the number of lesions also increase. Demyelination of the myelin sheath enhances the inflammatory activities that are responsible for cytokines release and antibody production, destroying the blood–brain-barrier (BBB) and stimulating macrophage activation (Balasa et al., 2021; Ionescu et al., 2023; Papiri et al., 2023). The myelin sheath destruction occurred together by infiltrating phagocytes, B-lymphocytes, plasma cells, and T-lymphocytes (Bogie et al., 2011). Microglia and macrophage activation is the tremendous cause of MS lesions. Activated microglia and macrophages combined with B and T cells have originated neuroinflammatory tissue damage (O'Loughlin et al., 2018; Spiteri et al., 2021). Generally, inflammatory activities inhibit the transfer of information in a CNS by; (i) antibodies and cytokines producing direct attacks on neurons to stop neurotransmitters, (ii) antibodies and cytokines increasing the damage of the myelin sheaths, and (iii) antibodies and cytokines together induced axonal damage (Koriem, 2016; Ludwin, 1995).

2.1. *Types of MS*

MS is classified into four main types depending on the development and progression of the disorder, which are as follows (Bechtel and Wong, 2012).

1. Relapsing-remitting MS (RRMS): This is the basic form of MS, affecting approximately 85 % of MS patients. RRMS is characterized by attacks of new neurological signs of decline or discomfort and then occurs at the time of partial or complete remission (Dolati et al., 2017).
2. Secondary-progressive MS (SPMS): This occurs in some patients diagnosed with RRMS. It is the first receptive-remitting disorder. SPMS initiates progressive impairment of neurological functions with or without capacity (Dolati et al., 2017).
3. Primary-Progressive MS (PPMS): About 15 % of MS patients have this disorder. There is no possibility of relapse or remission in PPMS (Rich et al., 2023)
4. Progressive-Relapsing MS (PRMS): Only 5 % of MS patients suffer from PRMS. It is increasing in the form of lesions, which indicate destruction in neurological functions and occasional replacement; there are no chances of remission (Maghzi et al., 2011; Rich et al., 2023).

3. Critically important anatomical structures and cell types

3.1. *Blood-brain barrier (BBB)*

Anatomically, BBB is located at the brain microvascular network

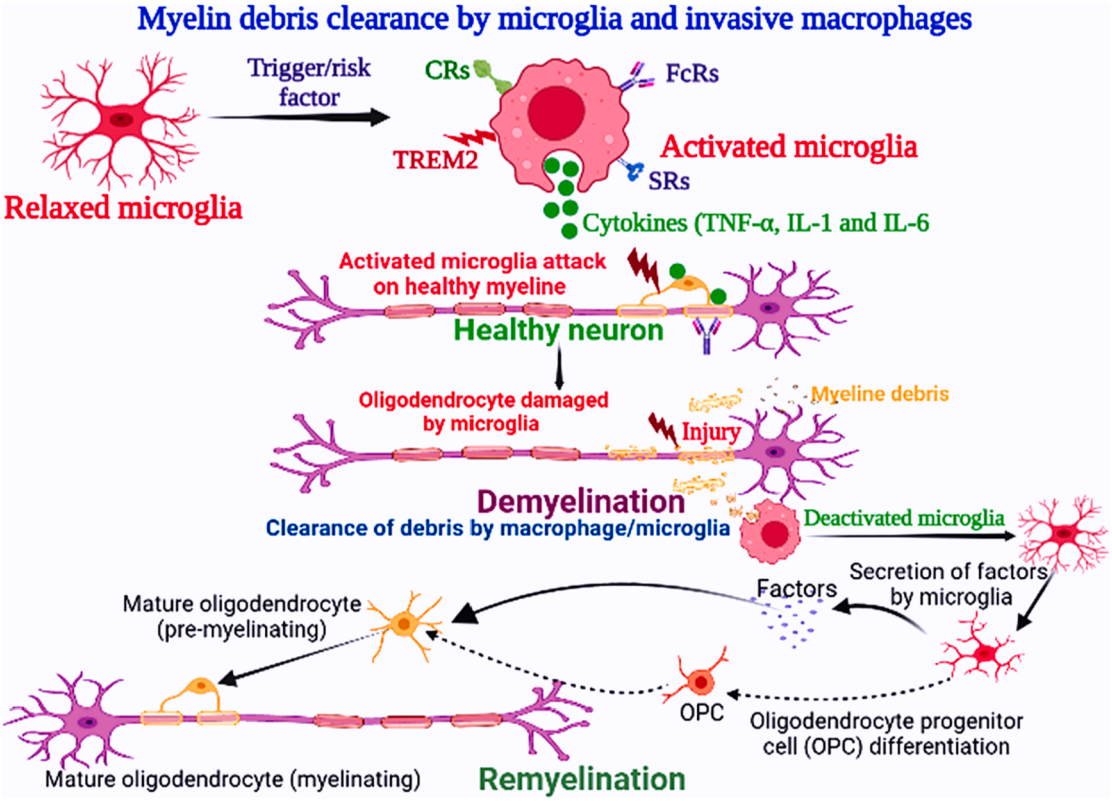

Fig. 3. Microglia-involved in myelin debris clearance and remyelination in MS: Microglia control remyelination following demyelination and aids in maintaining of oligodendrocyte precursor cells (OPC).

level comprising capillaries, arterioles, and venules. This barrier stops giant molecules, immune cells, and pathogens like bacteria and viruses from entering the central nervous system (CNS) from circulation (Ghasemi et al., 2017). For proper operation, the spinal cord and brain must meet specific conditions. The CNS's brain and nerve cells must be able to get oxygen and glucose from the blood while protected from infection and external hormone influences. Endothelial cells comprise the cell layer that lines all blood vessels, controls blood flow, and exchanges between surrounding tissues via the paracellular pathway. The endothelial cells in the brain and spinal cord are closely packed together, and chemicals can only get over the barrier through regulated transport channels or, in exceptional cases. Glial cells, including astrocytes, maintain the BBB (Kokare et al., 2020).

Multiple sclerosis is assumed to have been caused by a chain of events. An early step of this process is considered to include a blood–-brain barrier (BBB) breakdown. Immune cells can pass through the BBB if it is weakened or damaged in any manner. These cells then attack the myelin surrounding the nerves, resulting in nerve damage and MS symptoms (Balasa et al., 2021). The Janus-faced role of CD44/PG in activating microglia is evident today, which defends the CNS from foreign materials and restricts medicine's entry into the brain. However, CD44 was introduced early on as a promoter of immune activation and migration of activated inflamed substances across BBB. The BBB may be harmed or disturbed by various causes, such as stress, inflammation, or chemical responses thought to be triggered by sickness, medications, air pollution, or smoking. Research on the microbiome has investigated potential connections between gut health and BBB strength. Even treating neurodegenerative disorders is not accessible due to the hurdle of BBB and the Janus-faced behavior. Both help to defend the CNS and make treating MS more difficult.

3.2. *Microglia in mental disorders*

Microglia are a highly specialized population of mononuclear phagocytes that have been linked to yolk sac progenitors invading the neuroepithelium during fetal hematopoiesis (Prinz and Priller, 2014; Waisman et al., 2015). They are referred to as the CNS's resident immune cells; microglia may regularly renew themselves throughout an individual's life through coordinated apoptotic and proliferative mechanisms after they have been established in the CNS (Lloyd et al., 2017; Tay et al., 2017). In homeostatic situations, self-renewal is random, but in disease states, it is focused in response to local perturbations through site-specific clonal proliferation of microglia clusters. Microglia's primary purpose in the adult CNS is to supervise tissue homeostasis and perform surveillance tasks to guard against any threats to the integrity of the CNS (Tay et al., 2018). Due to their highly ramified and changeable shape, motility, and ability to penetrate the milieu, they can detect changes brought on by both endogenous and external signals.

The molecular mechanism exclusive to microglia and encoded by a collection of genes collectively known as the microglial sensory functions are responsible for this capacity (Chhatbar and Prinz, 2021; Sen et al., 2022). WM, which contains more microglia than gray matter, differs from gray matter (GM) regarding microglial cells' location, quantity, and phenotype (Martini et al., 2020). In addition to the identified core of some genes, genome-wide transcriptional profiling of microglia from diverse adult mouse brain regions has revealed that microglia have distinct transcriptional profiles that account for a significant amount of cellular heterogeneity (Murdock and Tsai, 2023). *Ex vivo* flow cytometric study has also demonstrated this, revealing variances in the expression of immunoregulatory proteins in various regions of microglia. Microglia can perform specific homeostatic activities thanks to the variety of their molecular repertoire, which may also account for the range of reactions they exhibit in pathological CNS conditions (Takata et al., 2021). One of the primary roles of microglia is

phagocytosis. Microglia use their phagocytic abilities to clear out extra neurons and synapses throughout development, especially in the early postnatal period, forming the structure of adult neural networks (Sen et al., 2022). The creation of trophic and synaptogenic factors also serves this purpose. Phagocytic microglia remove cellular detritus and pathogens in diseased situations to make a place for reparative processes. Microglia go through a process of cellular activation in response to injury and disease that is characterized by morphological modifications (such as amoeboid, enlarged, sphere-like cell bodies with shorter branching), increased cell proliferation, and functional modifications, including the production of soluble mediators (Tay et al., 2018). Depending on the time and location, these processes can have both negative and positive consequences and impact the neurological outcome. Single-cell transcriptome investigations have conclusively shown that, *in vivo*, microglia exist in a myriad of dynamic states that are continually changing, departing from the categorization that classified reparative microglia as M2 and destructive microglia as M1 (Lloyd et al., 2017). Microglia are the effectors of innate immune response and produce a range of chemotactic mediators that support the activation and trafficking of immune cells drawn to the site of injury (Prinz and Priller, 2014). They also develop the ability to deliver antigens by expressing costimulatory molecules such as cluster of differentiate 40 (CD40) and major histocompatibility complex II (MHC II).

3.3. Microglia in MS

The start and course of multiple sclerosis, a chronic inflammatory illness of the CNS, have been linked to the interaction of hereditary predisposition, environmental variables, and abnormal immune system activation, both innate and adaptive (Hemmer et al., 2015; Olsson et al., 2016). Clinical signs include tiredness, cognitive impairment, and sensory, visual, and motor abnormalities. The phenotypes of MS vary, but they are all defined by impaired BBB permeability, immune cell infiltration into the CNS parenchyma, and glial activation (Ghasemi et al., 2017; Sen et al., 2022). Fig. 3 represents microglia involved in myelin debris clearance and remyelination in MS. These incidents work together to cause and spread neuroinflammation, the development of demyelinating lesions, and eventually neurodegeneration. All phases and types of MS share the significant trait of microglial activation (Dolati et al., 2017).

Antigen-presenting cells in the CNS may be considered at the BBB level and in the CNS parenchyma. Competent antigen presentation at each location depends on cells expressing the necessary costimulatory and major histocompatibility complex (MHC) components (Jack et al., 2005). Perivascular macrophages are thought to be the primary antigen-presenting cells within the BBB. These cells are a form of systemic Trojan horse since they are produced from circulating monocytes that cross the BBB and have a high turnover rate. By having higher levels of CD14 and CD45 expression than parenchymal microglia, perivascular macrophages may be distinguished from them. Perivascular macrophages in both humans and animals exhibit MHC class II by default, and this expression is further increased in these cells in MS lesions. In fact, a thorough categorization of MS lesions to disease stage and development has been made possible by histological characterization of microglial morphology and the expression pattern of specific markers in normal and pathological settings (Hemmer et al., 2015; Stephenson et al., 2018). Microglia in the normal brain has high expression of homeostatic indicators such as the purinergic receptor P2RY12 and low expression of CD68, CD45, human leukocyte antigen-DR (HLA-DR) and MHC class II receptor molecules (Böttcher et al., 2020). In the early phases of lesion development, microglia make clusters or nodules in the normal-appearing white matter (NAWM); demyelination is absent. As pre-active or early active lesions, these formations are made up exclusively of microglia with elevated CD68, CD45, and HLA-DR (Miedema et al., 2020; Pettas et al., 2022). They are not accompanied by BBB changes or astrogliosis but are linked to degenerating axons. Here, pro-inflammatory and pro-repair markers are present in the microglia (e.g., production of tumor necrosis factor (TNF), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-2 subunits, and interleukin 10 (IL-10). Microglial processes are seen in intimate contact with transected axons in active WM lesions, where microglial activation is increased by additional overexpression of CD68, CD45, HLA-DR, and B7 (integral membrane protein) costimulatory molecule (Lloyd et al., 2017).

At this point, microglia lose their characteristic homeostatic expression, such as downregulating P2RY12 expression in favor of the inflammatory P2X7 receptor (Butovsky et al., 2015). In chronic active WM lesions, a hypocellular, demyelinated core is surrounded by a cluster of CD68 + microglia/macrophages containing residual lipids. Chronic, dormant demyelinated WM lesions are hypocellular and can still contain CD68 + microglia and macrophages (Plastini et al., 2020). A similar categorization based on microglia morphology has been developed for GM lesions, where microglial activity has been linked to cortical demyelination and neurodegeneration (Bevan et al., 2018). Here, microglial activation exhibits a gradient pattern, more significant in the cortex's superficial layers at the meningeal surface where GM damage is most severe and subsequently lessens in the cortex's deep layers (Gray et al., 2008). Microglia in active and chronic active MS lesions release a range of chemicals, which have been associated with both negative and neuroprotective roles, according to histological investigations on post-mortem MS tissue (Gray et al., 2008; Lubetzki et al., 2020). These cytokines include TNF and TNF family members, such as lymphotoxin and TNF-related weak inducer of apoptosis (TWEAK), as well as IL-1b, IL-6, IL-12, IL-23, and IL-33, all of which have mostly been linked to harmful inflammatory processes. In recent work, increased harmful TNFR1 signaling in neurons and oligodendrocytes has been directly linked to the development and severity of submeningeal GM lesions (Kaiser and Stäheli, 2014; Lubetzki et al., 2020). This is due to the loss of TNFR2-mediated protective TNF signaling in microglia. Microglia also generate chemokines, such as CC chemokine ligand (CCL) CCL4, CCL5, CCL8, CXC chemokine ligand (CXCL) CXCL9, CXCL10, CXCL2, and CXCL4, which aid in drawing T-lymphocytes and monocytes into the CNS (Janssens et al., 2018). Microglia in lesion locations have been shown to have increased expression of the C-C chemokine receptors CCR5, CCR8, and CXCR4, indicating that they react to chemoattractant signals to enter the demyelinating lesion environment (Cartier et al., 2005; Janssens et al., 2018).

Intriguingly, CCR5 + microglia with phagocytic morphology are present in early remyelinating lesions as well as active lesions, suggesting that this microglia population may be involved in both reparative and destructive phagocytic activity depending on the stage of the remyelination process (Trebst et al., 2008). Our understanding of the functional variety of microglia in the MS-affected CNS has changed significantly because of the application of single nucleus transcriptomics to post-mortem MS tissue. Microglia lose their homeostatic signature in and around lesion sites in the WM and GM and convert into a range of activated phenotypes such as overexpression of CD163, CD68, CD74, and macrophage scavenger receptor (MSR) that dynamically alter as the illness progresses (Van Wageningen et al., 2019).

In GM and WM, microglia have various gene signatures. Microglia controls the expression of genes related to glycolysis and iron homeostasis in GM. However, they enhance the expression of genes related to lipid metabolism in the WM, indicating that they have valuable functions in both regions (van der Poel et al., 2019). Additionally, it has been demonstrated that in MS, activated microglia participate in the tissue damage brought on by reactive oxygen species (ROS). In fact, both the WM and GM microglia within and close to MS lesions have been reported to have elevated levels of ROS-producing enzymes such as myeloperoxidase (MPO) and NADPH oxidase subunits (Bizzozero et al., 2005).

4. Experimental animal models

Since there are three primary animal models of MS, it is possible to understand essential aspects of human MS even though the immune systems of mice and humans differ significantly due to their different evolutionary histories (Denic et al., 2011). Recently, most studied animal models for MS are experimental autoimmune encephalomyelitis (EAE); Theiler's murine encephalomyelitis virus (TMEV) infection and subsequent chronic demyelination; and toxin-induced models of demyelination, including cuprizone and lysophosphatidylcholine-induced MS model (Elyaman and Khoury, 2017; Procaccini et al., 2015).

4.1. Significance and limitations of animal models in MS

Currently, no one animal model can accurately represent the whole range of variability of human MS and its diversity in clinical and radiological presentation since MS is a complicated illness (Hartung, 2008). However, the pathogenic processes of MS have recently been studied using animal models. The essential advantage is that they may be used as a testing ground for new treatment strategies and research on disease progression (Denic et al., 2011; Robinson et al., 2020). In contrast to human tissues, biopsies, or autopsy samples, which are infrequently done, are also a reasonably easy supply of tissue from the CNS, which is the major target of MS (Patergnani et al., 2017). Recently, various experts questioned whether these animal models might accurately represent MS, given that they do not precisely capture all facets of human disease (Sofroniew and Vinters, 2010). Animal models, for example, frequently use extremely artificial illness start methods (induced by active immunization with an autoantigen). Furthermore, the timing of the emergence of clinical symptoms differs between mice and humans (Ben-Nun et al., 2014; Van Brussel et al., 2014). When the illness is induced in animal models, symptoms might be seen weeks or even days later than in humans, where the physiological processes that underlie the disease are not seen for years before the start of clinical manifestations (Procaccini et al., 2015).

Furthermore, unlike any therapy for people, the treatment in these therapy trials began relatively early during the artificially generated autoimmune illness (Pearson et al., 2019). More significantly, most experimental studies utilized in bread are conducted on genetically homogeneous mice, and these mice frequently have genetic abnormalities that are highly challenging to detect in human populations (Procaccini et al., 2015). Although it has become clear that the immune systems of rodents and humans differ significantly because of their divergent evolutionary histories, they nonetheless share some fundamental concepts. In this case, three key animal models of multiple sclerosis allowed for comprehending pertinent aspects of human MS (Pearson et al., 2019). EAE, viral-induced models, particularly TMEV infection and subsequent chronic demyelination, and toxin-induced models of demyelination, including the cuprizone and lysolecithin models, are the most frequently used animal models of MS (Pontis et al., 2020).

4.2. Experimental autoimmune encephalomyelitis (EAE) in mice

The MS model most frequently used is EAE, myelin proteins such as MOG, MBP, and proteolipid protein have highly immunogenic areas that synthetic peptides can mimic to trigger the condition (Rangachari and Kuchroo, 2013). For immune activation, peptides are injected emulsified in Complete Freund's Adjuvant (CFA), and pertussis toxin is also typically administered. Pertussis toxin is hypothesized to encourage BBB disruption and enable immune cell extravasation into the CNS parenchyma. Because it is T cell-mediated, EAE is particularly well-suited to replicate the pathological features of the acute and relapsing-remitting phases of MS. This has led to the development of first-line disease-modifying therapies, which are already in use in clinical settings (Gerhauser et al., 2019). Like MS, EAE has severe immune-inflammatory activation maintained by the cooperative activity of local glia, particularly microglia, and immune cells trafficking into the central nervous system (Fig. 3).

In addition to the additional elevation of activation markers and a decrease in cell proliferation, the illness peak is CD40-dependent (Plastini et al., 2020). At this stage, encephalitogenic T cell proliferation and the ongoing infiltration of leukocytes that support the advancement of chronic diseases need CD40-dependent microglial activation. Notably, T cells directly affect microglial responsiveness by attaching to microglial CD40 in a positive feedback loop (Aarts et al., 2017). Studies show that IL-23, especially the p40 subunit, controls the microglial regulation of T cell encephalogenicity. EAE is inhibited without microglial p40 due to a change from a Th1 to a Th2 phenotype (Montilla et al., 2023).

Because CX3CR1 animals enable conditional gene deletion of the microglia-specific gene, several intracellular signals regulating microglial activation in EAE have been discovered. For mediating cellular activation, CX3CR1, which is primarily produced by microglia in the CNS, is essential (Goldmann et al., 2013). Increased microglial activation following its ablation coincides with an early EAE start and a more severe clinical outcome. The TGFb-activated kinase 1 (TAK1) is another significant signal for microglia activation and releasing proinflammatory IL-1b and CCL2 (Filippova and Nabors, 2020). As a result, there is decreased immune cell infiltration and demyelination and EAE is controlled.

In the wake of EAE, the nuclear factor kappa-activated B cells (NF-kB) regulatory protein also contributes to microglial activation. Its loss results in increased nod-like receptor protein 3 (NLRP3) inflammasome activity, increased IL-1b release and worsened neuroinflammation. Microglia increase the production of inflammatory mediators, such as cytokines (TNF, IL-1b, IL-6), chemokines (CCL1, CCL2, CCL5, CCL7, CXCL2), complement factors (e.g., C4a), and nitric oxide, as part of the activation process. Interferon-gamma (IFNg) and IL-17, released by T cells infiltrating the CNS, are at least partially responsible (Olcum et al., 2020).

Since its conditional ablation significantly improves EAE symptoms, immune cell infiltration, and demyelination, microglial IL-6 is pathogenic in EAE. This may be partly attributable to endothelial cell activation of IL-6 receptors (IL-6R), which disrupts the blood–brain barrier and increases immune cell trafficking in the central nervous system (Hendriksen et al., 2017; MacDougall et al., 2022). Similarly, the inflammasome pathway-blocking caspase-1 inhibitor VX-765 is therapeutic in EAE because it prevents the synthesis of the neurotoxic IL-1b and IL-18 generated by microglia. Similarly, growth factors produced by microglia support harmful CNS inflammation in EAE (McKenzie et al., 2018; Sharma et al., 2022). Microglia activate Transforming Growth-Factor-b (TGFb) upon Angiotensin II type-1 receptor (AT1R). Candesartan, an anti-hypertensive medication, blocked AT1R, which decreased TGFb synthesis and enhanced EAE, indicating that this class of molecules may have a therapeutic impact in MS. It should be emphasized that specific research implies TGFb roles in EAE are advantageous (Bild et al., 2022). However, the protective effects of this cytokine during EAE have not been examined in a cell-specific way. Therefore, it is unknown whether they depend on microglia or not. Microglial vascular endothelial growth factor B (VEGF-B) activates pro-inflammatory NF-kB signaling, upregulates NF-kB-dependent cytokines, and worsens EAE via inducing Fms-like Tyrosine Kinase 1 (FLT-1) signaling in astrocytes. Numerous signals, including the chemokine receptor 8 (CCR8) CCL1 axis, have been found to encourage harmful microglial activation in EAE in addition to cytokines (Li et al., 2022; Spence and Voskuhl, 2012).

In fact, CCL1, abundantly generated by microglia following EAE, maintains cell activation after EAE start by interacting with its cognate receptor CCR8, which is also expressed in microglia. It has been hypothesized that this process also operates in MS (Plastini et al., 2020). Toll-like receptor (TLR) signaling stimulation causes microglia to

Table 1
Features of the different multiple sclerosis animal models.

MS model	Mechanism	Application	Interacted cells	References
$PLP_{139-151}$ peptide to induce relapse-remitting EAE in C57BL/6J female mice	Caused the tissues of the spinal cord to become inflamed with numerous microglia infiltrates and clear demyelination.	Investigation of immune system activation and inflammation.	Macroglia, CD8, CD4, macrophages, B cells, and T cells	(Cong et al., 2020)
LPC associated MS	The myelin sheath in WM tracts is damaged by LPC solution's detergent action, and most mature myelinating oligodendrocytes are specifically killed by dissolving their membrane.	To study remyelination and demyelination in MS.	Macroglia, oligodendrocytes and astrocytes	(Buttigieg et al., 2023)
Cuprizone-associated MS in male Wistar rats	Feeding male Wistar rats with 0.6 % cuprizone for 2 weeks.	Analysis of the demyelination and remyelination in MS.	Macroglia, oligodendrocytes and astrocytes	(Gadhave and Kokare, 2019)
MOG_{35-55} peptide induced EAE in C57BL/6J mice	Immunization of C57BL/6J mice with MOG_{35-55} peptide.	Analysis of the neuroinflammation and degeneration in MS.	Monocytes, macrophages, B cells, Treg cells and microglia	(Croxford et al., 2011)
Ethidium Bromide induced EAE in mice model.	DNA intercalator that kills all live cells by preventing transcription and replication in the nucleus.	To study remyelination and demyelination in MS.	Macroglia, oligodendrocytes and astrocytes	(Buttigieg et al., 2023)
EAE in transgenic mice	B cell heavy chain knock-in mouse strain or T cell clone producing Vα and Vβ chains responding exclusively to MOG_{35-55}.	Analysis of the neuroinflammation and degeneration in MS.	B cells, monocytes CD8, CD4, and macrophages	(Luckey et al., 2011; Rangachari and Kuchroo, 2013)
TMEV-induced demyelination in C57BL/6 mice	Activation of microglia, T and B cells.	To study remyelination and demyelination in MS.	Microglia, B-lymphocytes, T-lymphocytes, astrocytes, and macrophages	(Gerhauser et al., 2019; Jin et al., 2019)

$PLP_{139-151}$: synthetic myelin proteolipid protein 139–151 fragment, *LPC:* lysophosphatidylcholine, *WM:* white matter, *MOG_{35-55}:* myelin oligodendrocyte glycoprotein 35–55, *Vα and Vβ:* non-restricted T cell receptor Vα and Vβ, *TMEV:* Theiler's murine encephalomyelitis virus, *EAE:* experimental autoimmune encephalomyelitis, *CD8 and CD4 cells:* cluster of differentiation 8 and 4 cells.

become activated and produces soluble mediators like TNF, IL-10, IL-6, CCL2, CCL5, and granulocyte–macrophage colony-stimulating factor (GM-CSF) (Turner et al., 2014; van Noort and Bsibsi, 2009). Among the several TLRs, 15-alphahydroxicholestene (15-HC), an oxidized cholesterol derivative detected in the serum of MS patients and animals with EAE, directly activates TLR2 (Liao et al., 2021). The adverse effects of neuroinflammation from TLR2 activation by 15-HC included worsened EAE symptoms and increased microglial production of CCL2, inducible nitric oxide synthase (iNOS), and TNF. The E3 ubiquitin ligase Peli1 was shown to control TLR signaling through the degradation of TRAF3 since its deletion prevented microglial activation and reduced EAE (Plastini et al., 2020). Through several pathways, microglial activation in EAE has been connected to direct impairment of neuronal function. It has been demonstrated that inflammatory mediators released by microglia, particularly TNF, replicate the synaptic changes in hippocampal glutamatergic transmission seen in EAE (Rizzo et al., 2018). Additionally, changes in synaptic and cognitive function following EAE were linked to ROS generated by microglia through the action of mitochondrial NADPH oxidase. Following EAE, aberrant glutamate transmission at Purkinje cell synapses was associated with microglia in the cerebellum (Kraft and Jean Harry, 2011). By pharmacologically deactivating microglia with the ribonucleotide reductase inhibitor didox, axonal damage in the cortex that was generated by interaction between activated microglia and the axon beginning segment responsible for action potential initiation may be reversed (Plastini et al., 2020). Reduced loss of postsynaptic structures was seen in response to inhibition of mixed lineage kinases, which have been linked to microglial activation and neurodegeneration. Significantly, disease-modifying medications used in MS therapy have demonstrated effectiveness in reversing synaptic impairment in EAE by inhibiting harmful microglial activation (Groves et al., 2013; Yong and Yong, 2021). Fumarates, which disrupt NF-kB signaling, as well as sphingosine-1-phosphate (S1P) receptor modulators like fingolimod, laquinimod, and ozanimod, which inhibit the production of proinflammatory mediators from microglia (such as TNF), are examples of these (Konen et al., 2023; Song, 2020). These findings show that overt and chronic microglial activation harms CNS autoimmunity and that inhibiting or avoiding this process may be beneficial.

4.3. Virus-causing Theiler's murine encephalomyelitis (TMEV)

However, till, no specific virus has been recognized as a possible cause or contributor to MS (Lipton et al., 2007). Epidemiological investigations have indicated that a viral infection earlier in life, in the existence of a particular genetic background, may cause an immune-mediated invasion against CNS (Bale, 2015). An Epstein-Barr virus (EBV) infection is currently associated with environmental MS risk (Carocci and Bakkali-Kassimi, 2012). Thaler's murine encephalomyelitis virus (TMEV) and several types of coronaviruses, such as mouse hepatitis virus, are the picornaviruses that have been most investigated for their ability to cause demyelination in mice (Ludlow et al., 2015). One of the neurotropic viral disease models for MS is TMEV, a positive-sense, non-enveloped, single-stranded RNA virus. Based on its capacity to harm the CNS, TMEV is split into George's disease 7 (GDVII) and Theiler's original (TO) subgroups (Procaccini et al., 2015; Sato et al., 2011). For mice, the GDVII subgroup, which includes the strains GDVII and FA, is extremely neurovirulent because it causes mortality within 1 to 2 weeks (Tsunoda and Fujinami, 2010). Acute polio encephalomyelitis is brought on by the TO subgroup's Daniels (DA) and BeAn8386 (BeAn) strains (Procaccini et al., 2015; Sato et al., 2011; Velloso et al., 2012). Unlike EAE, the condition is invariably chronic-progressive in susceptible mice, and TMEV can only cause inflammatory demyelinating illness in mice and not in other species like rats or primates (Bröer et al., 2017; Donati and Jacobson, 2014). According to Tsunoda and Fujinami (2010), the GDVII virus primarily affects neurons, and dying nerve cells exhibit chromatin condensation and apoptotic (fragmented) nuclei (karyorrhexis) in the lack of activation of inflammatory mononuclear cells (Tsunoda and Fujinami, 2010). Unlike GDVII infection, DA infection causes parenchymal, perivascular, and sub-arachnoid MNC infiltrates that are composed of CD3 T cells during the critical phase, whereas during the chronic phase (a minimum of thirty days after infection), the inflammation in GM of the CNS subsides (Oleszak et al., 2003; Tsunoda and Fujinami, 2010).

Although the axonal injury is shown in MS and its animal model EAE, it is thought that severe inflammatory demyelination, in which lesions form from the outside (myelin) to the inside, is the primary cause of axonal damage (Witte et al., 2014). Nevertheless, in TMEV infection, axonal damage is caused before demyelination (inside-out model), and the distribution of injured axons seen in the initial stage correlates to

Table 2
Available therapies and disease-modifying therapies for MS.

Drug	Brand name	Mechanism of action	Route of Administration	Reference
Fingolimod	Tascenso ODT®	Sphingosine-l-phosphate receptor modulators.	Oral	(Aktas et al., 2010; Ingwersen et al., 2012)
Teriflunomide	Aubagio®	Limitations the expansion of rapidly multiplying B and T cells by inhibiting the pyrimidine synthesis pathway.	Oral	(Confavreux et al., 2014)
Dimethyl fumarate	Dimethyl Fumarate	Improves the density of Th2, triggers the anti-oxidative stress response, hampers NF-kB activation, and affects apoptosis in lymphocytes.	Oral	(Mills et al., 2018)
Monomethyl fumarate	Bafiertam™	Improves density of Th2, triggers the anti-oxidative stress response, hampers NF-kB activation, and affects apoptosis in lymphocytes.	Oral	(Berger et al., 2021; Mills et al., 2018)
Cladribine	Mavenclad®	Stops the B cells from reaching into the brain and spinal cord, hence cannot damage the myelin sheath.	Oral	(Berger et al., 2021)
Siponimod	Mayzent®	Selective sphingosine-1-phosphate receptor modulator.	Oral	(Goodman et al., 2019)
Ponesimod	Ponvory™	Sphingosine-1-phosphate receptor modulator.	Oral	(Baldin and Lugaresi, 2020; Ruggieri et al., 2022)
Diroximel fumarate	Vumerity®	It works as an immunosuppressant and anti-inflammatory agent.	Oral	(Paik, 2021)
Ozanimod	Zeposia®	Sphingosine-1-phosphate receptor agonist, confines lymphocytes to peripheral lymphoid organs and keeps them from congregating in the areas of their organs that are chronically inflamed.	Oral	(Linker and Gold, 2013)
IFN beta-1a	Avonex®	Controls B and T cells, decrease BBB interference and normalizes cytokine functions.	Intramuscular/ subcutaneous	(Dhib-Jalbut and Marks, 2010)
IFN beta-1b	Betaseron®	Controls B and T cells, decrease BBB interference and normalizes cytokine functions.	Intramuscular/ subcutaneous	(Dhib-Jalbut and Marks, 2010)
IFN beta-1b	Extavia®	Controls B and T cells, decrease BBB interference and normalizes cytokine functions.	Intramuscular/ subcutaneous	(Dhib-Jalbut and Marks, 2010)
Glatiramer acetate (GA)	Copaxone®	Hampers the binding of T cells to MBP and different myelin antigens, influences tolerance, improves the number of Th2 cells and Tregs, and reduces the number of Th17 cells.	Intramuscular/ subcutaneous	(Lalive et al., 2011)
GA -generic equivalent of Copaxone 20 mg and 40 mg doses	GA Injection	Hampers the binding of T cells to MBP and different myelin antigens, influences tolerance, improves the number of Th2 cells and Tregs, and reduces the number of Th17 cells.	Intramuscular/ subcutaneous	(Lalive et al., 2011)
GA-generic equivalent of Copaxone 20 mg and 40 mg doses	Glatopa®	Hampers the binding of T cells to MBP and different myelin antigens, influences tolerance, improves the number of Th2 cells and Tregs, and reduces the number of Th17 cells.	Intramuscular/ subcutaneous	(Lalive et al., 2011)
Ofatumumab	Kesimpta®	Provide immediate B cell depletion.	Intramuscular/ subcutaneous	(El Mahdaoui et al., 2022)
Peginterferon beta-1a	Plegridy®	Reduces MS regressions and the advancement of disability and brain lesions related to MS by decreasing inflammation, specifically, IFN-beta reduces antigen production and T cell multiplication.	Intramuscular/ subcutaneous	(Neuhaus et al., 2006)
IFN beta-1a	Rebif®	Controls B and T cells, decrease BBB interference and normalizes cytokine functions.	Intramuscular/ subcutaneous	(Neuhaus et al., 2006)
Ublituximab	Briumvi™	B-lymphocytes connect to cells on their surface, which causes cell lysis via processes such complement and antibody-dependent cellular cytolysis.	Intravenous infusion	(Lee, 2023)
Alemtuzumab	Lemtrada®	Immediate and long-lasting deficit of B cells, T cells and monocytes.	Intravenous infusion	(Havrdova et al., 2015; Ruck et al., 2015)
Mitoxantrone	Novantrone®	Cytotoxic impact on B cells and T cells.	Intravenous infusion	(Neuhaus et al., 2006)
Ocrelizumab	Ocrevus®	It targets the CD20 marker on B-lymphocytes and is an immunosuppressive medication.	Intravenous infusion	(Lamb, 2022)
Natalizumab	Tysabri®	Controls the leukocytes to cross the BBB by interacting with integrins.	Intravenous infusion	(Brandstadter and Sand, 2017)

Th2: type II helper T cells, *NF-kB*: nuclear factor kappa activated B cells, *BBB:* blood–brain-barrier, *Tregs:* regulatory T cells, *Th17:* T-helper 17, *MBP:* myelin basic protein, *IFN-beta:* interferon beta, *CD20:* cluster of differentiate 20.

locations where later inflammatory demyelination takes place during the chronic stage (Procaccini et al., 2015) (Table 1). This data implies that axonal degradation initiates T cells and macrophage migration into the brain, which results in further myelin loss.

4.4. Toxic MS simulations

It is possible to undertake viral-induced demyelination as well as lethal demyelination in contrast to the well-studied experimental method for inducing demyelination in mice, such as autoimmune inflammatory-induced demyelination in EAE (Psenicka et al., 2021a, Psenicka et al., 2021b) (Table 1). Harmful demyelination is a better option for studying these and remyelination processes, even if EAE is the most used model to represent the autoimmune genesis of MS. Cuprizone and lysolecithin are the two substances that are used to cause demyelination the most frequently (McMurran et al., 2019; Schultz et al., 2017; Sun et al., 2012).

4.4.1. Cuprizone-induced animal demyelination model

Additionally, to cause oligodendroglial cell damage and consequent demyelination, cuprizone, a copper-chelating chemical, also significantly activates microglia and astrocytes in rodents (Gudi et al., 2014) (Table 1). Cuprizone only targets adult oligodendrocytes that cannot meet the high metabolic requirement and thus experience apoptosis. Whereas the other cell types are unaffected (Pandur et al., 2019; Praet et al., 2014). Due to cuprizone's ability to chelate copper, the copper shortage is the primary cause of metabolic failure. However, it is yet unknown why only oligodendrocytes are now sensitive to these side effects (Benetti et al., 2010). Shortly after removing cuprizone from the diet, fresh oligodendrocytes begin forming a new myelin sheath after demyelination is complete. These cells are produced from a pool of oligodendrocyte progenitors (OPC) (Zirngibl et al., 2022). At the same time, cuprizone's experimental utilization, the precise mechanism of action, and the cause of oligodendrocyte injury are poorly understood. Administering copper along with cuprizone did not lessen the harmful

effects. Therefore the copper-chelating ability of cuprizone does not appear to be the primary mechanistic explanation (Gudi et al., 2014; Praet et al., 2014). Although swollen "giant" mitochondria are seen in cuprizone-induced mice's liver and brain, there is significant proof that oligodendroglial apoptosis primarily depends on mitochondrial disturbances (Zirngibl et al., 2022). Recently, cuprizone-treated oligodendrocytes cultured *in vitro* showed significantly decreased in mitochondrial potential. Thereby, a significant quantity of oxygen and adenosine triphosphate (ATP) is required to maintain a significant membrane synthesis (Sun et al., 2012; Zirngibl et al., 2022). A cuprizone-treated model is an excellent tool for examining fundamental processes throughout demyelination and remyelination without predominantly immune-mediated events, but not ideal for studying autoimmune-mediated demyelination (Pandur et al., 2019). When cuprizone is constantly consumed, remyelination fails, and demyelination lasts until the diet is finished (chronic demyelination). Gadhave and Kokare (2019) developed the teriflunomide-loaded nanostructured lipid carriers and tested them against the cuprizone-induced rat demyelination model (Gadhave and Kokare, 2019). In this instance, the remyelination capability is maintained after stopping the cuprizone diet but significantly reduced.

4.4.2. *Lysolecithin-associated demyelination*

Lysolecithin injected into the spinal cord of various species, such as rabbits, rats, mice, and cats, leads to activating phospholipase, causing specific regions of demyelination (Table 1). Instead of subsequent impacts on oligodendrocytes, demyelination results from the primary harmful effects on myelin sheath (Bjelobaba et al., 2018). Despite significantly harming nearby cells or axons, lysolecithin causes a quick and highly repeatable kind of demyelination in the CNS; this process is not immune-mediated because it also occurs in immune-deficient animals (Lassmann and Bradl, 2016). Nevertheless, if young animals are employed, chronic inflammation in lesions is negligible, and full remyelination takes place in 5–6 weeks; on the other hand, healing in older animals is substantially slower (Denic et al., 2011). B cells, Neutrophils, T cells, and macrophages infiltrate lesion locations in the acute phase right after the lysolecithin injection, and these cells appear to be engaged in brain healing (Fisher et al., 2022; Wang et al., 2018). Following hours after administration, macrophage and microglial infiltration and activation start, and they continue for several days. It is unclear exactly what part these cell types play in creating the conditions necessary for remyelination (Kong and Gao, 2017; Xiong et al., 2016). It is widely acknowledged that the T cell response encourages macrophages and astrocytes to express several neutrophils, supporting neurons' survival and preservation. Many growth factors are generated during the remyelination process, and T cells may boost oligodendrocyte remyelination either directly or indirectly by increasing the activity of CNS glia (Kong and Gao, 2017). Further evidence that macrophages play a crucial role in the cycle of myelin repair is provided by the impairment of perse oligodendrocyte remyelination caused by macrophage reduction (Franklin and Ffrench-Constant, 2017; Keough and Yong, 2013). All this information revealed that toxin-induced demyelination models, as compared with EAE and virus-induced demyelinating syndrome, are employed solely to study the process of demyelination and remyelination and do not mimic MS sickness (Procaccini et al., 2015).

5. Modified therapies in MS

Currently, different disease-modifying therapies are used for relapsing forms of MS. Modified multiple sclerosis therapies are classified into two distinct groups: oral and intravenous therapies.

5.1. *Oral therapies*

Oral delivery was discovered in treating mental disorders like MS because they are easy to prepare, administer, and enhance patient compliance. Table 2 represents the available treatments and disease-modifying therapies for MS via oral, intramuscular/subcutaneous, and intravenous routes. Fingolimod is the first oral medicine, which was approved by the US-FDA in 2010 for the treatment of MS. Fingolimod directly acts on sphingosine-1-phosphate receptor-1 that leads to the degradation of receptors (Groves et al., 2013; Ingwersen et al., 2012). This mechanism of fingolimod decreases the concentration of activated lymphocytes in the blood and protects from neurodegeneration.

Another oral remyelinating medication in the management of RRMS is known as Aubiago (Teriflunomide). Teriflunomide is a potent inhibitor of dihydroorotate dehydrogenase (DHODH), which exhibits anti-inflammatory action and reduces the growth rate of stimulated immune responses (Gadhave and Kokare, 2019). Teriflunomide typically prevents dihydroorotate (DHO) from becoming orotate, inhibiting the pyrimidine de novo synthesis pathway and preventing nucleic acid production (Gadhave and Kokare, 2019). Teriflunomide was approved by US-FDA in 2014 for treating a mental disorder like MS (Bayas and Mäurer, 2015; Miller, 2015). Furthermore, teriflunomide has hindered the proliferation of stimulated astrocytes, microglia, T, and B-lymphocytes by obstructing the synthesis of immune-modulating agents such as cytokines. Recent research articles revealed that the available TFM formulation exhibited hepatic and renal toxicities (Birceanu et al., 2014; Gadhave et al., 2021a, Gadhave et al., 2019b).

Dimethyl fumarate is a recently approved oral medicine for the therapy of MS treatment (Callegari et al., 2021). Dimethyl fumarate was used to treat patients with psoriasis (Narapureddy and Dubey, 2019). The mechanism of this medicine is cleaved and absorbed as monomethyl fumarate, which increases the apoptotic stimulation of lymphocytes (Prosperini and Pontecorvo, 2016). The reported side effects of this medicine are vomiting, diarrhea, nausea, flushing, and abdominal pain. Dimethyl fumarate effectively lowered the recurrence rate of Th1 and Th2 hyperintense lesion burden. However, its mechanism of action remains to be fully understood. According to previous research, dimethyl fumarate has been shown to have neuroprotective and immunomodulatory properties. Dimethyl fumarate administration causes apoptosis in T cells, according to in vitro studies. Nine dimethyl fumarate-treated individuals had a lower fraction of memory CD4 + and CD8 + T cells and produced less proinflammatory cytokine. According to animal investigations, dimethyl fumarate also suppresses nuclear factor kappa B (NF-kB) in activated T cells and mouse bone marrow-derived dendritic cells (DCs). By decreasing intracellular glutathione, dimethyl fumarate produces a type II DC phenotype that produces less IL-12 and IL-23.

In April 2020, the US Food and Drug Administration (FDA) approved monomethyl fumarate, an active metabolite of dimethyl fumarate, for treating adults with relapsing MS, including active secondary progressive and relapsing-remitting disease. Oral delayed-release capsules containing 95 mg are used for administration. After taking a 190 mg twice-daily maintenance dosage for seven days, the beginning dose is 95 mg twice-daily. Monomethyl fumarate is the active metabolite of dimethyl fumarate. It is believed to alleviate oxidative cell damage and inflammation by activating NF-kB and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (Mills et al., 2018). By way of the transcriptional target, oxidative stress-induced growth inhibitor 1 (OSGIN1), Nrf2 activation by monomethyl fumarate was shown to protect against cytotoxicity in human astrocytes. In addition, the expression of vascular cell adhesion molecules is downregulated by monomethyl fumarate, inhibiting monocyte adherence and transendothelial migration across an inflamed human blood–brain barrier (BBB). Monomethyl fumarate can alter the immunological response by hindering dendritic cell development and Th1 cell activation. Monomethyl fumarate also has a neuroprotective impact on ischemia–reperfusion in rats when the Nrf2 pathway is activated. The mechanism of action is yet uncertain, much like with dimethyl fumarate and its active metabolite monomethyl fumarate (Berger et al., 2021).

Cladribine is an oral medication used to treat multiple sclerosis. The dose that has received FDA approval is 3.5 mg/kg given over two years,

or 1.75 mg/kg annually. There is a twelve-month gap between the two therapy sessions. The initial course is administered in the first month over four to five consecutive days. In the second month, an equivalent dose is administered over four to five consecutive days. Cladribine is a deoxyadenosine analog with a chlorine atom in place of a hydrogen atom at position two of the purine ring, making it resistant to adenosine deaminase (ADA) deamination. The selective disruption of T-cell (cell-targeting) and B-cell (humoral) immunity resembles severe immunodeficiency disease. High cladribine concentrations cause the expression of deoxycytidine kinase to rise within cells, which causes lymphocyte death. Low intracellular levels of cladribine promote phosphatase 5′-nucleotidase, which inactivates phosphorylated (active) cladribine. The phosphorylated form of cladribine affects intracellular activities by suppressing DNA synthesis/repair, ribonucleotide enzymes, and alternating endonuclease activity. Cladribine targets active immunity to suppress these immunological reactions. Clinically and radiographically, the medication lessens MS patients' disease burden (Balasa et al., 2021; Berger et al., 2021).

Siponimod, a medication developed by Novartis for the treatment of MS, also referred to as Mayzent. The FDA authorized it on March 26, 2019. This medication is a sphingosine-1-phosphate (S1P) receptor modulator and is hypothesized to reduce MS-related inflammation of the central nervous system. A sphingosine-1 phosphate (S1P1) modulates various physiological processes by attaching to G-protein-coupled receptors (S1P1-S1P5). The S1P receptors are mainly found in lymphocytes, oligodendrocytes, astrocytes, erythrocytes, eyes, and the spleen, and they control heart rate, smooth muscle tone, endothelial barrier function, and cellular trafficking. Within six hours of the initial dosage, it reduces the peripheral blood lymphocyte count dose-dependently. This is brought about by the reversible buildup of lymphocytes in lymphoid tissues because of the absence of a lymphocyte release label. As a result, the inflammation linked to multiple sclerosis is reduced. 90 % of patients see a recovery to normal lymphocyte counts within 10 days of the end of medication (Goodman et al., 2019).

Ponesimod is the FDA-approved, selective sphingosine 1-phosphate receptor 1 modulator used to treat people with relapsing types of multiple sclerosis. Ponesimod was developed in response to the demand for a more focused sphingosine 1-phosphate receptor 1 modulator than fingolimod (Baldin and Lugaresi, 2020). On the surface of lymphocytes, the sphingosine 1-phosphate receptor 1 (S1P1R) is expressed and recognizes sphingosine 1-phosphate (S1P) at nanomolar concentrations. Sphingomyelin, a component of cell membranes, produces the metabolite S1P. Gradients of S1P concentration are produced by lymphocytes in response to S1P1R agonism when sphingomyelin degrades. Higher S1P levels in the blood and lymph cause lymphocytes to depart the lymphoid organs. Ponesimod alters this response by enhancing and internalizing the S1P1R on lymphocytes, rendering them blind to variations in S1P concentration and lowering the number of lymphocytes in circulation (Ruggieri et al., 2022).

FDA authorized diroximel fumarate in October 2019, developed by Alkermes and Biogen. Despite being bioequivalent to dimethyl fumarate, this medication has a different chemical structure, making it less prone to gastrointestinal adverse effects. How this medication treats MS still needs to be fully understood (Paik, 2021). It is only thought that diroximel fumarate controls the cell signaling pathways, resulting in positive immunological and neuroprotective benefits. The active metabolite of diroximel fumarate is monomethyl fumarate which in humans stimulates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathways (Narapureddy and Dubey, 2019; Paik, 2021). In response to oxidative stress, this mechanism is activated in cells. Additionally, monomethyl fumarate is an agonist of the nicotinic acid receptor in a lab environment. At this moment, it is unclear how this discovery may be used to treat MS. According to the theory, this drug's lack of methanol, leaving the group in its chemical structure and substitution with inert 2-hydroxyethyl succinimide is what causes it to have less gastrointestinal side effects.

Ozanimod was approved on March 26, 2020, by US-FDA for the MS. Inflammatory bowel disease (IBD) and relapse MS are both treated with ozanimod, a once-daily sphingosine 1-phosphate receptor modulator. The G-protein-coupled receptor subtypes known as S1P1-5R are bound by the significant phospholipid sphingosine-1-phosphate (S1P), which is present in the body (Rasche and Paul, 2018; Ruggieri et al., 2022). S1P regularly maintains the immunological, cardiovascular, pulmonary, and neurological systems; the receptors it binds to S1P can be expressed almost everywhere, which is crucial for controlling inflammation. The central nervous, immunological, and cardiovascular systems include S1P1R, S1P2R, and S1P3R receptors. S1P4R is present in lymphocytic and hematopoietic cells, but S1P5R expression is limited to the spleen (on natural killer cells) or the central nervous system. Ozanimod binds to the S1P1R and S1P5R subtypes of S1P receptors and selectively modulates these receptors. Ozanimod's exact mode of action is unknown, although it is thought to work by preventing lymphocytes from migrating as much, which would otherwise exacerbate MS-related inflammation (Linker and Gold, 2013).

Other oral MS medicines like laquinimod have under examination (Narapureddy and Dubey, 2019; Wynn et al., 2020). That is a new orally approachable carboxamide derivative developed for relapsing-remitting and chronic progressive MS (CPMS) (Lin et al., 2021). The treatment of mental disorders via the oral route is a somehow challenging task due to the first-pass effect, lower aqueous solubility, higher dissolution time, and, most important an obstacle of BBB (Kamma et al., 2022; Thöne and Linker, 2016). All these physiochemical barriers have dominated the scientists working in this area. Solid oral dosage forms such as tablets and capsules do not easily bypass the BBB due to their large particle size and first-pass effect. Hence, an alternative route or dosage form is needed to treat MS (Gadhave et al., 2021a; Upadhyay, 2014; Zhao et al., 2021).

5.2. *Intravenous therapies*

Self-injectable treatments are "first-line therapy" in the medical community (Table 2). Interferon (IFN) beta-1a (Avonex, Rebif, Plegridy) and IFN beta-1b (Betaseron) are commonly used IFN medicines that are administered intramuscularly or subcutaneously on a daily or weekly basis (Gilli et al., 2018; Hauser and Cree, 2020). IFN-b controls cytokine release modifies T and B cells and lowers BBB disruption. Although these medications reduce recurrence rates and the development of incapacity, they are also associated with several side effects (Annibali et al., 2015; Hendin, 2018). Glatiramer acetate (GA, Copaxone, cop1) poly[Y,E,A,K]n, [L-tyrosine, L-glutamic acid, L-alanine, and L-lysine]n, is a self-injectable medication made up of a copolymer of four amino acids from the myelin basic protein (MBP) sequence that autoreactive T cells identify (Dolati et al., 2017). Copaxone, when given subcutaneously, reduces the risk of relapse and disease progression in MS patients (Annibali et al., 2015; Hendin, 2018). GA blocks T-lymphocytes from adhering to MBP and other myelin antigens, resulting in tolerance induction. GA also increases the number of helper T cells type II (Th2) and regulatory T cells (Tregs) while decreasing the number of Th17 cells (Farina et al., 2002). IFNs and GA are presently the most widely used therapies, and they are equally beneficial in both children and adults in reducing MS relapses by 30 % (Bakshi et al., 2013).

Irritation is the most common adverse effect of IFN and GA injections when administered subcutaneously (90 %) or intramuscularly (33 %) (Krueger et al., 2016). As a result, injectable dosages including intravenous, intramuscular, and implant medications, are directly exposed to systemic circulation and cause-related adverse effects. These drugs failed to bypass the BBB and limited therapeutic concentrations delivered to target sites (English and Aloi, 2015). Therefore, these formulations are not a perfect solution for treating MS, necessitating further therapy.

Table 3
Different animal models are used to study nanoparticles to treat neurodegenerative disorders, multiple sclerosis.

Type	Animals	Nanoformulations	Drugs	Route of administration	Reference
Experimental autoimmune encephalomyelitis	C57BL/6 J female mice	Solid lipid nanoparticles	Dimethyl fumarate	Oral	(Bevilacqua Rolfsen Ferreira da Silva et al., 2022)
Cuprizone-induced microglia activation demyelination using Elevated plus maze model	Male Wistar rats	Nanostructured lipid carriers	Teriflunomide	Intranasal	(Gadhave and Kokare, 2019)
Experimental autoimmune encephalomyelitis	Male Lewis rats	Liposomes	Methylprednisolone	Intravenous	(Gaillard et al., 2012)
Experimental autoimmune encephalomyelitis	Lewis rats	Liposomes	C16-angiopoietin	Intravenous	(Fu et al., 2023)
Experimental autoimmune encephalomyelitis	Female C57BL/6 J mice	Exosomes	Resveratrol	Intranasal	(Zheng et al., 2023)
Experimental autoimmune encephalomyelitis	Female Dark Agouti rats	Peptide functionalized polymeric nanoparticles	Antibodies	Intravenous	(Führmann et al., 2015)
Experimental autoimmune encephalomyelitis	C57Bl/6 Mouse Model	PLGA Nanoparticles	Myelin oligodendrocyte glycoprotein	Intravenous	(Gholamzad et al., 2021)
Cuprizone-induced MS and lysolecithin induced MS models	Mice	Gold nanoparticles	CNM-Au8	Oral	(Robinson et al., 2020)
Experimental autoimmune encephalomyelitis	Female C57BL/6	Gold nanoparticles	Gold nanocrystals with polyethylene glycol	Intraperitoneal injection	(Aghaie et al., 2019)

6. Biomaterials in MS therapy

Many different types of nanoformulations have been created so far; among them are nanoemulsions, dendrimers, lipid-based nanoparticles (LB-NPs), polymer-based nanoparticles, and nanoparticles made of polymers. These can effectively target the CNS with enhanced drug release mechanisms (Gadhave et al., 2023; Gastaldi et al., 2014; Lueshen et al., 2015). After surface functionalization, nanomaterials can function in the CNS and transport medications via the BBB. They can significantly increase the concentration of medications in the brain and prevent reticuloendothelial system phagocytosis, which makes drugs available over the BBB and has grown into a crucial element of both primary and applied research on how drugs are delivered (Fornaguera et al., 2015). Different biomaterials utilized in the therapy of MS are depicted in Table 3 and Fig. 4, respectively.

6.1. Lipid nanoparticles

Lipid nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions are thought to be the best means for delivering therapeutic medicines against MS to the CNS while improving brain circulation. They can penetrate the brain's capillary endothelial cells and cross the BBB, lessening their adverse effects on nearby tissues.

6.1.1. Solid lipid nanoparticles (SLN)

Solid lipid-based nanospheres with a typical 50–1000 nm diameter composes the SLN. They are made up of a solid lipid matrix, such as fatty acids and glycerol, or waxes, which are strengthened by emulsifiers that are compatible with human physiology, such as phosphatidylcholine, bile salts, Tween, polyoxyethylene ethers, or polyvinyl alcohol. Ojha et al., reported that hot emulsion ultrasonication was used to effectively develop DMF-loaded SLN and a 3-level 3-factor Box-Behnken design via RSM was used to optimize it. The three independent factors' combined effects were examined, and it was discovered that they considerably influenced the dependent answers. The findings of an *in vitro* investigation indicated that the cumulative drug release was 82 % and that roughly 40 % of the drug was released in the first 180 min, which led researchers to believe that SLNs would be a good choice for improving the management of the multiple sclerosis condition (Lueshen et al., 2015) (Table 3).

6.1.2. Nanostructured lipid carriers (NLC)

NLC's is a good potential category of lipids nanocarriers, which can quickly enter the CNS. The NLC formulation uses tiny droplets (less than 100 nm in size) of a composition with outstanding biocompatibility, biodegradability, and safe transporters to increase the adequate quantity of medication in the intended cells (Gadhave et al., 2019a). Moreover, the NLC approach incorporates liquid lipid into the solid lipid matrix, enhancing its capacity for drug loading and entrapment (Alam et al., 2013; Ojha and Kumar, 2018). Intranasal nanolipid vehicles containing TFM, an inhibitor of dihydroorotate dehydrogenase with anti-inflammatory properties, were recently developed by Gadhave et al., (Gadhave and Kokare, 2019). TFM-loaded NLCs were produced using melt emulsification ultrasonication technology, and the composition was finalized using the Box-Behnken statistical analysis (Table 3).

6.1.3. Liposomes

In fundamental and clinical research, liposomes, lipid-based nanoparticles (LB-NPs), are frequently used as drug delivery systems (DDS) to overcome suboptimal efficacy. Regarding treating MS, some research teams have already created DDS medications and have successfully demonstrated both a prolonged blood concentration of the active ingredients and a therapeutic impact on MS model animals. To identify immune cells involved in the progression of MS, Shimizu et al., created drug-encapsulating liposomes with an autoantigen added to the surface. The encapsulation of cytotoxic medication was carried by the autoantigen-modified liposomes to the autoantigen-recognizing CD4 + T cells in the spleen, killing them and preventing the emergence of clinical symptoms brought on by an inflamed neurological deficit in the CNS (Shimizu et al., 2021), The *in vivo* animal model for liposomes is depicted in Table 3.

6.1.4. Fusogenic liposomes

Phospholipid liposomes have been used as carrier particles to transfer proteins and peptides into active mammalian cells directly. Such liposomes are typically ingested by endocytosis, during which the bulk of their payload is destroyed in lysosomes before reaching their target site (Kube et al., 2017). A recently developed molecular carrier system, fusogenic liposomes, was employed to transfer proteins. These liposomes effectively merged with the cellular plasma membrane when encountering mammalian cells. They were filled with water-soluble proteins, conveying the liposomal content to the cytoplasm without degrading. The low liposomal concentration and a very short incubation

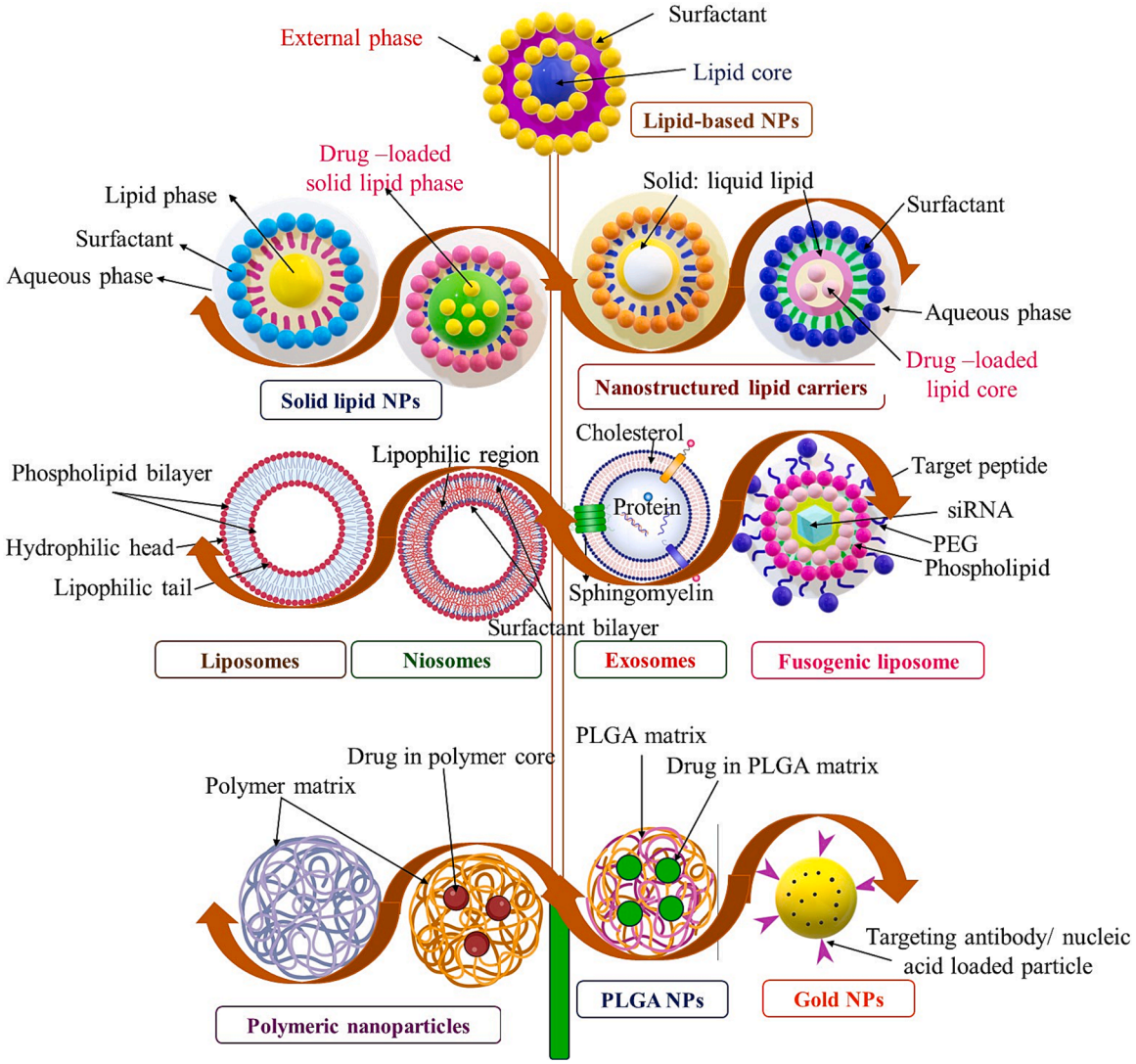

Fig. 4. Representation of the utilization of different biomaterials/nanocarriers in treating MS: lipid-based nanoparticles (LB-NPs) with an inner phase composed of lipid or oil and an outer phase of water and drug entrapped in the internal phase, which is stabilized with surfactant. Certain LB-NPs, such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, exosomes, and new generation LB-NPs, i.e., fusogenic liposomes, are currently and will in future use for drugs, vaccines, siRNA, miRNA, and protein delivery in MS. Similarly, other biomaterials such as polymeric, PLGA and gold nanoparticles are highly preferable in the treatment of MS. PLGA and polymeric nanoparticles are composed with biodegradable polymers and drug has encapsulated within the polymer matrix. Gold nanoparticles have medicinal properties and carry different therapeutics like antibodies and nucleic acids.

time of a few minutes prevent the usual cell toxicity of a positively charged lipid component and help to penetrate the targeted cell. Recently, Wiedenhoeft et al. successfully developed fusogenic liposomes for resveratrol brain delivery and determined their efficacy in aged mice (Wiedenhoeft et al., 2019). The findings of this experiment were fascinating because they showed the protective effects of drug-loaded fusogenic liposomes on endothelium-dependent relaxation in the aorta. Hence, these novel nanocarriers are highly applicable to delivering biological therapeutics to the brain (Gadhave et al., 2021b) to treat neurodegenerative disorders, i.e., MS.

6.2. *Polymeric nanoparticle*

In polymeric Nanoparticles, solid colloidal carriers, the medicament or physiologically active substance is immersed, encapsulated, entrapped, coupled, or adsorbed on macromolecular polymers (Fornaguera and Solans, 2016). These pharmaceutical NPs function via endocytosis or transcytosis through the brain endothelium to penetrate the BBB and transport it to the Central nervous system (Chountoulesi and Demetzos, 2020). At the molecular level, polymeric materials can easily target and can be released effectively (Fig. 4). They enable structural changes to achieve targets and are also cost-effective. Polyurethanes, poly(e-caprolactone), poly(lactide-co-glycolide), and poly(lactide-co-glycolide) (PLGA) are consistently cited materials for microRNA (miRNA) administration to treating MS (Neuberg and Kichler, 2014).

6.3. *PLGA nanoparticles*

The widely used non-toxic, biodegradable polymer is poly (lactic-co-glycolic) acid, which is biocompatible and approved by the US regulatory agency (Butreddy et al., 2021). Therapeutic approaches for MS are based on various mechanisms of immune cells, immune suppression and tolerance, and inflammation and remyelination process (Nuzzo and Picone, 2021). Apart from the above, remyelination failure is a serious problem with MS disease progression. Fibronectin plays an important role in forming aggregates, thereby inhibiting the lesion environment at the site of remyelination. So, novel therapeutic approaches also target lesion sites to overcome remyelination failure (van Schaik et al., 2022).

As described above, MS is characterized by demyelination of neurons due to patient's immune system. To achieve immune tolerance, specific antigen therapies that work on the immune cells are emerging as novel therapies. Considering this, Lima et al., encapsulated a proteolipid protein (PLP) protein, an important protein of the myelin sheath into PLGA nanoparticles. The prepared nanoparticles were found to be stable. After this, they incorporated these nanoparticles into polymeric microneedle patches that can be administered via skin. Based on the characterization and *in vitro* release study results, these authors conclude that the developed formulation can be administered through a negligible invasive route (Lima et al., 2020). Similarly, Iro et al., developed myelin peptide analogues based on mouse/rat epitope 35–55 of myelin oligodendrocyte glycoprotein (MOG) encapsulated PLGA nanoparticles. Further, these were conjugated with glucosamine to target the mannose receptors of the dendritic cells. Additionally, these nanoparticles were found to be effective in reducing the inflammation of the central nervous system based on the results from the experimental autoimmune encephalomyelitis (EAE) animal model of MS. So the authors conclude that these nanoparticles could be an alternative and potential approach to induce the immune system tolerance against the MS disease progression (Triantafyllakou et al., 2022). Falling on similar lines, in a study, the researchers encapsulated leukemia inhibitory factor (LIF) in PLGA particles. LIF, a vital stem cell growth factor is required for central nervous system health due to its tolerogenic, myelinogenic and neuroprotective properties. Further, it is decorated with CD4 to increase the targeting of lymphocytes. The authors conclude from the in vivo pharmacokinetic and pharmacodynamic studies that these nanoparticles cross the BBB and demonstrate a specific anti-inflammatory response in the brain's frontal cortex and acceptable safety upon intravenous administration (de la Flor et al., 2021). Further, Interferon beta-1a intramuscular injection reduces the symptoms of MS by reducing inflammation and nerve damage. Based on this, in a study, Kardos et al., synthesized interferon-beta-1a loaded PLGA and pegylated PLGA nanoparticles with high encapsulation efficiency (>95 %). Although these nanoparticles were not toxic from the *in vitro* studies, they demonstrated mild toxic effects including pale kidney and pyelectasis in the *in vivo* Wistar male rats. The authors conclude that this mild toxicity could be due to renal infiltration due to their smaller size; further studies are needed to understand the efficacy and toxicity profile (Fodor-Kardos et al., 2020). Also, as mentioned earlier, by encapsulating the protein-based inverse vaccines, i.e., MOG 35–55 autoantigen and recombinant IL-10 into PLGA nano/microparticles and tested their efficacy *in vitro* and C58BL/6 mice model of MS. These nanoparticles significantly reduced the course of autoimmune encephalomyelitis (EAE) and reduced the histopathologic lesions in the central nervous tissue that ultimately helps in the successful remyelination (Cappellano et al., 2014). In a study, the authors encapsulated dimethyl fumarate into PLGA nanoparticles. Fumaric acid esters have a huge potential in MS. The authors chose dimethyl fumarate for this study. Further, these nanoparticles were coated with anti-CD40 monoclonal antibodies. The efficacy of anti-CD40mA-DMF-PLGA nanoparticles on the expression of inflammatory mediators such as IL-1β, TNF-α and IL-6 genes in mouse splenocytes. After treatments with nanoparticles, the expression of these mediators was significantly reduced. Based on these findings, the authors hope these targeted nanoparticles will provide a promising alternative therapeutic strategy to reduce neuroinflammation in MS (khosravi et al., 2021). In addition to the above, other potential therapeutic approaches for MS include the delivery of PLGA nanoparticles and PLGA nanoparticles embedded in chitosan microparticles via nose-to-brain delivery (Spindler et al., 2021). Also, encapsulating a novel phosphodiesterase 7 enzyme (that acts as a cellular messenger) analog, phenyl-2-thioxo-(1H) quinazoline-4-one into PLGA nanoparticles (Nozal et al., 2021). These delivery systems are yet to be tested in pre-clinical models (Table 3).

6.4. Exosomes in MS treatment

Exosomes and cells secreted extracellular vesicles are contributed to the movement of bioactive molecules such as nucleic acids, proteins, lipids, and metabolites. Thus, exosomes are involved in intercellular communication (Kalluri and LeBleu, 2020). These exosomes can also cross the blood–brain barrier and have the advantages of low immunogenicity and encapsulating drugs (Sun et al., 2022). So, they can be used in drug delivery systems. In addition, incorporating any biomaterials into these vesicles might result in new tissue-specific therapeutic outcomes (Ojeda-Hernández et al., 2022). For MS, exosomes are being investigated in research as novel markers to indicate the MS disease state and as a drug carrier system and the details are presented below. In a study, serum, cerebrospinal fluid, and peripheral blood mononuclear cell samples were collected from 75 multiple sclerosis patients and 45 healthy individuals. After that, from the collected samples, exosomes were isolated and central nervous system myelin protein contents were analyzed using enzyme-linked immunosorbent assays and western blot studies from the separated exosomes. Interestingly, exosomes that were extracted at non-central nervous system tissue expressed myelin proteins and the myelin oligodendrocyte glycoprotein presence associated with the MS disease state. Based on this, the authors conclude that exosomes might serve as novel markers of disease activity (Galazka et al., 2018). In a study, the authors extracted the exosomes from macrophages related to central nervous system microglia. Further, they have prepared resveratrol-loaded exosome formulations simultaneously. The authors have tested the efficacy of these resveratrol-loaded exosomes in a mouse model of MS via intranasal administration. Based on the anti-inflammatory response of the formulation at the central and peripheral nervous systems, the authors concluded that exosome formulation might provide a potential therapeutic option and, thus, recommended its development (Zheng et al., 2023). Further, in a study, the authors isolated the exosomes from mesenchymal stem cells that belonged to the human adipose tissue. Followed by MS disease was induced in SJL/J mice (a new inbred strain of mouse) by Theiler's murine encephalomyelitis virus (TMEV). Further, upon intravenous administration of exosomes to these mice, improved motor deficits, reduced brain atrophy, increased cell proliferation, decreased inflammatory infiltrates and increased myelin protein expression were observed. Thus, the authors recommend further studies to establish this approach for MS therapy fully (Laso-García et al., 2018).

6.5. Gold nanoparticles in MS treatment

Gold nanoparticles have anti-inflammatory and remyelinating properties as well as good encapsulating properties. Based on the anti-inflammatory property of gold nanoparticles, in a study, the authors conjugated these nanoparticles to ethylene dicysteine diethyl ester (ECD). Further, these were tested in C57BL/6 female mice that have developed the experimental MS. The animals treated with 0.6 mg/kg of ECD-conjugated gold nanoparticles showed improved clinical symptoms, inflammatory infiltrate and myelin integrity and improvements in clinical signs of the disease (Souza et al., 2021). Further, to test the remyelinating properties of gold, the authors prepared clean-surfaced, faceted gold nanocrystals in a study. They have demonstrated remyelinating properties against chronic cuprizone and acute lysolecithin-induced animal models of demyelination. Moreover, the prepared gold nanocrystals also enhanced the motor functions in mice. In this study, remyelination is confirmed through the expression of myelin differentiation markers in oligodendrocyte precursor cells and upregulated myelin-synthesis-related genes in central nervous system cells. Based on this study, these authors conclude that gold nanocrystals have a potential property of remyelination for MS. As mentioned earlier, MS remyelination failure happens because of MS lesions. Peptide nidogen-1 expression rises at these lesions. Laminin creates a stable complexation towards nidogen-1 through a heptapeptide. Based on this, the authors

Table 4
Clinical trials using gold nanoformulations as therapeutic agents in MS.

Trial Number	Sponsor	Disease	Device	Year of initiation	Year of completion	Number of enrolments	Status	References
NCT03536559 (VISIONARY-MS)	Clene Nanomedicine Clean Australia Ltd.	Relapsing MS	CNM-Au8	2018	2022	150	Terminated (COVID-19-related enrollment challenges) Phase-II	(Clene Nanomedicine, 2023a)
NCT03993171 (REPAIR- MS)	Clene Nanomedicine Texas Southwestern Medical Center	Relapsing MS	CNM-Au8	2019	2021	30	Active (recruiting) Phase-II	(Clene Nanomedicine, 2023b)
NCT04626921 (VISIONARY-LTE)	Clene Nanomedicine George Clinical.	Relapsing MS	CNM-Au8	2020	2024	150	Active (not recruiting)	(Clene Nanomedicine, 2023c)

LTE: long term extension; *MS:* multiple sclerosis.

have used targeted therapy to avoid remyelination failure and promote remyelination. They employed gold nanoparticles further and were conjugated to this heptapeptide to target the MS lesion areas. To study the efficacy of these gold nanoparticles, demyelination is induced by injection of lysophosphatidylcholine in adult male C57BL/6J mice (Ta). From the results of enhanced delivery of the heptapeptide functionalized gold nanoparticles, and enhanced myelin content and reduced astrocyte/ microglia activation, the authors concluded that this peptide is useful to target the lesions in MS patients (Farhangi et al., 2023).

6.6. Nanoformulations-based therapies under clinical trials

It is accepted that bulk gold is chemically inert; however, recent studies have shown that gold can be a robust catalytic material at the nanoscale (Robinson et al., 2020). The conversion of nicotinamide adenine dinucleotide hydride (NADH) to nicotinamide adenine dinucleotide (NAD) is one of the body's fundamental processes. Adenosine triphosphate (ATP) synthesis, oxidative phosphorylation, and glycolysis depend on the redox partners NAD and NADH. Moreover, NADH oxidation depends on the central nervous system's (CNS) myelination process, which requires much energy. Given that GNPs enhance the oxidation of NADH to NAD, this route has been investigated for its ability to induce remyelination in neurodegenerative illnesses. Clene Nanomedicine has created the unique clean-surfaced, faceted gold nanocrystal preparation known as CNM-Au8 (Clene Nanomedicine, 2023a). Oligodendrocyte precursor cells were treated with gold nanocrystals under in vitro investigations, and the results included oligodendrocyte maturation and the expression of myelin differentiation markers. In addition, CNS cells responded to gold nanocrystals by producing more NAD, ATP, and lactate within and outside the cell and upregulating genes involved in myelin production. The intense remyelinating activity was also seen in mouse models following oral administration of gold nanocrystals.

Nanocrystalline gold is also in clinical trials. A total of 36 clinical trials with nanocrystalline gold are ongoing or completed as of today. Out of these 36, 13 trials were completed, 21 were ongoing, and 2 were terminated for administrative reasons. Both studies were terminated due to administrative reasons. Details about one trial are given below. A phase 2 clinical study (NCT03536559) was initiated to assess the efficacy and safety of gold nanocrystal (CNM-Au8) as a remyelinating therapy for vision-impairing MS lesions in participants with chronic vision problems because of relapsing-remitting MS (Clene Nanomedicine, 2023a). However, because of the enrollment issues due to covid-19 pandemic, this is one trial of two that has been terminated (Table 4). Epidermal growth factor (EGF) that could help in the remyelination process will have a tremendous therapeutic potential in MS. To encapsulate EGF, the researchers have utilized the advantages of gold nanoparticles. A study combined EGF into gold nanoparticles and administered via intracerebral route into C57BL6/J mice with demyelinated neurons. From the rotarod test that evaluates the motor coordination and myelin-associated protein levels such as 2′3′-cyclic nucleotide 3′-phosphodiesterase (CNPase), myelin-associated glycoprotein (MAG), MOG and MBP through western blot test, these authors conclude that EGF-associated gold nanoparticles as a promising therapy (Lira-Diaz et al., 2022). In addition to designing two more clinical studies, REPAIR-MS (NCT03993171), the University of Texas Southwestern Medical Center is also focused on the relapse of multiple sclerosis and Parkinson's disease (Clene Nanomedicine, 2023b). Participants who complete this experiment will continue in the VISIONARY-LTE study (NCT04626921), an open-label, long-term extension study (Table 4). As many of these studies' findings are expected to be published in the upcoming years, evidence supporting CNM-Au8′s effectiveness and safety may encourage the future growth of GNPs as a traditional medical intervention. Extension studies are now being created because of positive CNM-Au8 trials (Clene Nanomedicine, 2023c). Hence, biomaterials have an extensive future to treat the demyelinating severe disease, multiple sclerosis.

7. Concludable remarks

Nowadays, several innovative and potential drug delivery methods are being designed to precisely administer different therapies into diseased tissues without causing adverse consequences. Orally given medication delivery methods often positively impact patient compliance since they reduce the dosage frequency. The discovery of innovative treatment strategies for MS will continue to rely heavily on the animal model of EAE as a first-line model system, particularly for illuminating specific mechanistic issues. Nonetheless, many animal models created for MS have received persistent criticism, frequently leading to discouraging failures. It is crucial to remember that no animal model can capture the whole range of MS variability, and the field of research lacks a specific disease model for progressive MS. The humanization of the entire immune system in rats, which is now progressing, will undoubtedly offer significant benefits for investigating novel immunomodulatory strategies in more suitable models to address the complexity of MS. In treating CNS-related illnesses, nanomedicine holds promise for overcoming the drawbacks of existing traditional MS therapies. Nanomaterials that can target lesions and transfer drugs more efficiently show promise as a promising therapeutic approach for the near future.

CRediT authorship contribution statement

Dnyandev G. Gadhave: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization, Writing – review & editing. **Vrashabh V. Sugandhi:** Writing – review & editing. **Chandrakant R. Kokare:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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