Review

The Beneficial and Debilitating Effects of Environmental and Microbial Toxins, Drugs, Organic Solvents and Heavy Metals on the Onset and Progression of Multiple Sclerosis

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Abstract: Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system is common amongst young adults, leading to major personal and socioeconomic burdens. However, it is still considered complex and challenging to understand and treat, in spite of the efforts made to explain its etiopathology. Despite the discovery of many genetic and environmental factors that might be related to its etiology, no clear answer was found about the causes of the illness and neither about the detailed mechanism of these environmental triggers that make individuals susceptible to MS. In this review, we will attempt to explore the major contributors to MS autoimmunity including genetic, epigenetic and ecological factors with a particular focus on toxins, chemicals or drugs that may trigger, modify or prevent MS disease.

Keywords: MS; toxins; EAE; environmental; natural; microbial

Key Contribution: The article is a concise but comprehensive reference for most of the environmental and microbial toxins as well as drugs, organic solvents and heavy metals that can have an impact on the onset and progression of multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) affects the central nervous system ‘CNS’ that leads to focal plaques of primary demyelination and diffuse neurodegeneration in the grey and white matter of the brain and spinal cord [1]. Most MS cases are under the category of relapse-remitting disease that is, disease attacks are followed by recovery and stability periods [2]. Both pathological and radiological findings point to an early coexistence of neuroinflammation and neurodegeneration [3]. MS is one of the world’s most common neurologic disorders that leads to disability in young adults [4]. Approximately 2.5 million people worldwide suffer from MS, which is common in young adults, especially women [5]. This poses a major personal and socioeconomic burden with approximately 50% of patients requiring permanent use of a wheelchair [6]. MS is a complex and indecipherable disease and thought to be multifactorial, influenced by genetic as well as environmental factors [7]. Although an experimental model exists, it does not explain the variable clinical, pathological or immunological features of the disease [8]. MS management modalities have changed radically over the years to include not only disease-modifying therapies but also focusing on relapses and disability accrual prevention [9]. However, very little is known about the causes of MS disease. It remains much the same as during the
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time of William Boyd, who stated in 1958: “The amount of time and money which has been expended to determine the causal factors in multiple sclerosis is beyond computing . . . the result has been nil” [10].

2. Involvement of the Immune System in MS Disease

Immune mediated pathogenesis plays a significant role in MS [11], despite the strong barriers that restrict immune cells from reaching the immune-privileged CNS [12]. Whether MS is an autoimmune disease in its classical definition or inflammation associated demyelinating disease with some autoimmune manifestations remains a matter of controversy between different experts in the field, where each side showed their evidence in order to support or refute the autoimmune hypothesis [3].

The finding that half of MS immune function related genetic variants are shared with other putative autoimmune diseases makes the autoimmune model more acceptable [6,7]. Many recent publications referred MS as a prototypic autoimmune CNS disease [8–10], with autoimmune-mediated myelin injury in a susceptible host [11]. In such autoimmune model, autoreactive adaptive immune cells infiltrate and potentiate damage within the CNS [12]. CD4+ T cells are widely considered major players in the pathogenesis of MS [7]. CSF enrichment of functionally altered T helper cells (subtypes Th1 and Th17) and Treg cells as well as other leukocyte populations such as natural killer (NK) cells is documented in MS cases [13]. These lymphocyte skew towards a proinflammatory profile along with functional defects in the T and B regulatory subsets [14]. The autoreactive Th17 cells may pass the blood brain barrier or ‘BBB’ aided by IL-17 and IL-22 cytokines that disable tight junction proteins and endothelial cells, resulting in an influx of neutrophils leading to neuronal damage [15]. Pathogenic Th17 cells have low FasL expression, allowing them to escape the programmed cell death and persist in inflamed sites [16]. It was suggested that bystander activation upon viral infection can generate such autoreactive and potentially encephalitogenic T helper (Th)-1/17 cells which were recruited to the CSF following MS attacks [14]. Beside these identified players, new immune cells, like Interleukin (IL)-9 producing CD4+ T helper cells ‘Th9’ [17] and T helper 22 ‘Th22’ cells [18], which facilitate disease initiation or progress have been discovered. Moreover, recently CD8+ T cells were identified in MS lesions more than CD4+ T cells where their clones were found to be still present in blood and CSF after several years [7].

The study of B cell populations in MS plaques revealed an accumulation of clonally expanded B lymphocytes indicating the pivotal role of B cells, antibodies and its complement in the demyelination process [19]. Moreover, dendritic cells which act as antigen presenting cells (APCs) in addition to being effector cells in neuro-inflammation exacerbate MS pathology but the complete understanding of APCs role in human MS is still incomplete [7]. Based on these observations, the effect of environmental factors on genetically susceptible people is of immense need as it may initiate the cascade of damage.

Despite the fact that MS is not an inherited disease, family case clustering of MS is prevalent amongst first-degree relatives who have similarities in their major histocompatibility complex (MHC) such as HLA DR15/DQ6 allele, alleles of interleukin-2 receptor alpha gene ‘IL2RA’ and interleukin-7 receptor alpha gene ‘IL7Ra’ [20]. Furthermore, some MS patients showed specific single-nucleotide polymorphisms in such genes [21]. It was also noted that these loci are related to the immune system and hence could possibly make individuals prone to autoimmune diseases.

Genetic predisposition only explains a fraction of the disease risks [22]. Although by now more than a hundred genes are known to increase the risk of MS, these only contribute marginally [23]. Therefore, there must be another explanation for MS initiation. The parent-of-origin effect (i.e., the phenotypic effect of an allele depends on whether it is inherited from an individual’s mother or father) and the higher female-to-male ratio in MS are linked to the epigenetic X-chromosome inactivation and imprinting which have no susceptibility genes [21] indicating the importance of studying the epigenetic changes in such patients. In MS, epigenetic mechanisms are shown to affect T cell functions where histone acetylation was reported to occur in the white matter,
hyper-methylation in oligodendrocyte survival genes and hypo-methylation in proteolytic processing genes [24]. Moreover, epidemiological data shows an interplay between genetic susceptibility and the environment by modulating the epigenome of the immune system [21]. Such epigenetic mechanisms readily respond to environmental factors [25,26].

Even though genetic or epigenetic factors may lead to autoimmunity, there might be an initial trigger that could help researchers understand the pathogenesis of the disease. A summary of such triggers that can have beneficial and debilitating effects on the onset and progression of multiple sclerosis is listed in Table 1 and illustrated in Figure 1.

**Table 1. Beneficial and Debilitating Effects of Environmental and Microbial Toxins, Drugs, Organic Solvents and Heavy Metals on the Onset and Progression of Multiple Sclerosis.**

| Environmental and Microbial Toxins, Drugs, Organic Solvents and Heavy Metals | Beneficial Effect | Debilitating Effect |
|---|---|---|
| **1. Environmental and Geographical Factors** | | |
| • Geographic latitude | Yes | |
| • Sun exposure as a vitamin D source | Yes | |
| • Circadian disruption and sleep restriction | Yes | |
| **2. Toxic Effects of Lifestyle Habits** | | |
| • Smoking | Yes | |
| • Obesity and fatty acids intake | Yes | |
| • Ketogenic diet | Yes | |
| **3. Toxic Effects of Food, Diet and Gut Microbiota** | | |
| • Coffee | Yes | |
| • Alcoholic beverages and fish | Yes | |
| • High sodium intake | Yes | |
| • Vitamins | Yes | |
| • Probiotics | Yes | |
| **4. Toxic Effects of Microbes** | | |
| • Epstein Barr virus (EBV) infection | Yes | |
| • Bacterial toxins include staphylococcal, nasopharyngeal normal flora | Yes | |
| • Clostridium perfringens epsilon toxin*ε-toxin,* | Yes | |
| • Pertussis toxin (PTX) and botulinum toxins | Yes | ? Yes |
| • Aspergillosis | Yes | |
| • Mycotoxin ochratoxin A | Yes | |
| • Candida species | Yes | |
| **5. Chemicals, Organic Solvents and Heavy Metals** | | |
| • Pesticides and mothballs | Yes | |
| • Occupational chemical exposure | Yes | |
| • Heavy metals (mercury, lead, arsenic) | Yes | |
| • Copper | Yes | |
| • Zinc | Yes | Yes |
| **6. Drugs** | | |
| • ShK, a toxin from the sea anemone (Stichodactyla helianthus) and scorpion venom | Yes | |
| • Snake venoms | Yes | |
| • Thalassophryne nattereri Brazilian fish venom | Yes | |
| • Glatiramer acetate, fingolimod (FTY720), mitoxantrone, IFN-β, fumaric acid esters and corticosteroids | Yes | |
| • Tetanus toxoid vaccination, antibiotics, antihistamines and antifungal agents | Yes | |
environment by modulating the epigenome of the immune system [21]. Such epigenetic mechanisms readily respond to environmental factors [25,26].

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3. Toxic Effects of Environmental and Geographical Factors

Environmental influences modify disease risk and progression, possibly through epigenetic changes which could up- or down-regulate the immune response and influence neural development [23,27]. Exposure to organic solvents, work shift, alcohol, high coffee consumption [22,28], infections, sun exposure/vitamin D and smoking were linked to MS disease development [29], nevertheless, there is still insufficient evidence to establish a causal role [30].

MS is unevenly distributed throughout the world and increases progressively with geographic latitude with pockets of high MS frequency [31]. People in certain communities showed concerns about clusters of MS; and the role of environmental elements in the development of the disease was investigated extensively, although no conclusion was reached [32]. For example, Key West in Florida has an unusually high prevalence of multiple sclerosis [33]. Also, MS is more prevalent in the northern parts of Great Britain and Northern Ireland than in England and Wales [34], suggesting strong links between geography and the incidence of this disease [35]. This is further supported by a study in Canada where MS prevalence differs according to the region, suggesting that these differences may be due to environmental factors [36]. On the other hand, some studies have reported that the north/south variation in the prevalence of MS could be possibly due to a change in the genetic predisposition of these populations to MS [37].

Among many environmental factors, sun exposure as a vitamin D source plays a vital role. There is a consistent finding in many epidemiological studies that the risk of MS is higher in areas with low levels of sun exposure and hence low vitamin D status [38,39], thus suggesting that vitamin D is a modifiable risk factor for MS [40]. This bolsters the idea of the protective effects of vitamin D intake on the risk of developing MS [41]. Studies reported that treatment with vitamin D₃ improves clinical symptoms in the experimental autoimmune encephalomyelitis “EAE” mouse model [42]. It has been stated that low concentrations of neonatal vitamin D are associated with an increased risk of MS [43]. For instance, individuals born in November have significantly reduced incidence rate, linked to high levels of neonatal vitamin D exposure during the third trimester of pregnancy as a protective factor against multiple sclerosis [44]. Besides, vitamin D receptor (VDR) expression is hindered in MS and has been found to be regulated by the environment, genetics and epigenetics factors [45]. Increased vitamin D binding protein in the sera of MS patients exacerbate the pathophysiology of the disease [46]. It has
been demonstrated that ultraviolet radiation may attenuate Th1-mediated immune responses [31] or may decrease the secretion of the immuno-stimulatory neurohormone melatonin from the pineal gland [47].

On the other hand, circadian disruption and sleep restriction can disturb the melatonin secretion and hence enhance pro-inflammatory responses. This might provide an explanation for multiple studies that link MS with age and work shifts [48,49], where a statistically significant association was reported between shift work at age 15–19 years and MS risk [50,51]. Hence, lifestyle and environmental factors are key contributors to the risk of MS [22]. Consequently, further research should focus on establishing the potential roots of MS disease by investigating the lifestyle habits (diet, physical activity) of patients and their role in the pathogenic pathways [29].

4. Toxic Effects of Lifestyle Habits

An important risk factor for MS can be exposure to smoking [52] which may accelerate MS disease progression and disability [53]. Also, continued smoking is associated with an acceleration in time to secondary progressing MS [54]. The risk is further multiplied in HLA-DRB1*15 smokers due to a specific T-cell response to smoke that can aggravate the genetically regulated macrophage response [55]. Cigarette smoking is thus emerging as a modifiable risk factor for MS [56]. Family history of MS should be a warning sign for the family individual who smokes, where such a habit may aggravate or increase the chances of developing the disease [57].

On the other hand, there is strong evidence regarding the role of obesity during adolescence as a risk factor increasing MS [22,56]. There is also documented links between the incidence and severity of MS and fatty acids intake [58], as polyunsaturated fatty acids ‘PUFAs’ tend to reduce the frequency of relapses over two years [59]. Additionally, ketogenic diet can exert protective effects, likely via attenuation of the immune response and increased oxidative stress [60].

5. Toxic Effects of Food, Diet and Gut Microbiota

In studies of MS in animal model, high consumption of coffee was found to possibly decrease the risk of developing MS by suppressing the production of proinflammatory cytokines [61] due to the neuroprotective properties of caffeine [62]. Conversely, consumption of alcoholic beverages and fish are associated with the progression of the disability in relapsing onset MS disorder [63]. Likewise, high sodium intake can lead to an exaggerated clinical and radiological disease activity in patients with MS [64]. Besides the impact of vitamin D$_3$ consumption, there is no strong evidence regarding the benefits or risks of other vitamins in the onset or progression of MS [65].

Furthermore, differences in diet, vitamin D$_3$ insufficiency, smoking and alcohol consumption may affect the composition of the gut microbiota [66]. Gut microbiome is defined as all the microbial contents including genes, proteins and metabolic products in the gut at specific time [67]. Any disruption in the gut microbiota or so called “dysbiosis,” has been linked with several diseases [68]. In MS patients, the human gut microbiome exhibited variations in their composition and hence could be a cause or ameliorating agent in MS [69]. Furthermore, gut dysbiosis was found to increase intestinal and BBB permeability via microbiota-gut-brain axis, which could be restored upon intake of probiotics [70]. In this regard, improved hygiene influences autoimmune disorders highlighting the role and impact of gut flora on the development of EAE in mice [71].

6. Toxic Effects of Microbes

Water-damaged environments contain a complex mixture of contaminants produced by mould, Gram-negative and Gram-positive bacteria [72]. Such environment could be a site of chronic biotoxins that can lead to a cluster of MS-like illness cases [73]. Also, numerous infectious agents play a role in the onset of MS [74], as different viruses may trigger inflammatory demyelinating diseases resembling MS [75]. For instance, it has been reported that the timing of the primary Epstein Barr virus (EBV)
infection at a certain age in individuals who are genetically susceptible, plays a major role in the development of the disease [76].

Bacterial toxins include staphylococcal, nasopharyngeal normal flora and many others that can distort immunity and cause toxic damage in the nervous system. It has been reported that staphylococcal toxins stimulate human T lymphocytes, leading to activation of the myelin autoantigens, the myelin basic protein and the proteolipid peptide. This results in reactive T lymphocytes that contribute to the demyelinating disease in humans [77]. It is worth mentioning that the CSF and extracellular fluid circulation are bi-directionally linked through a route by which products of nasopharyngeal infection may drain into the CNS and be processed by the immune cells of the meninges, which in turn may trigger brain damage [78]. Another bacterial toxin is the clostridium perfringens epsilon toxin “ε-toxin,” where upon systemic administration, CNS white matter changes due to swelling of the myelin sheaths through the direct binding of ε-toxin to white matter. Blanch M et al. identified the myelin and lymphocyte (MAL) protein to be a key protein that could possibly mediate the cytotoxic effect of ε-toxin in inflammatory autoimmune diseases such as MS [79]. Furthermore, ε-toxin can cross the blood-brain barrier and precisely binds to myelinated fibres [80,81]. This leads to injury to oligodendrocytes or myelin, presenting a unique cellular target for ε-toxin in the CNS [82]. A study by Wagley et al. demonstrated an association between the presence of Clostridium perfringens ε-toxin and MS in the US population [83].

Pertussis toxin (PTX) and botulinum toxins are other bacterial toxins that have a great effect in MS. PTX exerts various effects in EAE mice, attenuating demyelination by about 75%. Furthermore, PTX reduces lymphocyte infiltration, deactivating microglia activation and changing T cell profile by increasing T helper type 1 and 2 as well as T regulatory cells [84]. Persistent PTX treatment is defensive from CNS autoimmune disease through upregulation of regulatory cytokines and expansion of CD4+CD25+FoxP3+ Treg cells. Multiple studies have reported that the bacteria-derived toxin, pertussis toxin, is known to lower susceptibility to EAE, despite the fact that its injection is needed to induce disease in some strains of mice [85,86]. On the contrary, botulinum toxin paralyzes muscles and is used as a traditional treatment of spasticity [87]. It was reported that this neurotoxin might improve the quality of life for many patients with MS [88,89].

Certain pathogenic fungi sequestered in non-neuronal tissues and release toxins that target astrocytes and oligodendrocytes causing myelin degradation and triggering MS [90]. Additionally, the secretion of different necrotizing factors in cerebral aspergillosis, can induce brain lesions and damage vital cells [91]. The food-associated mycotoxin ochratoxin A, exerts deleterious effects on numerous cell types including astrocytes [92]. Candida infection was found to be associated with increased odds of MS [93]. Several reports showed that MS patients might have antibodies against different Candida species [94], suggesting that this fungal infection may be a risk factor for MS [95]. Furthermore, C. Albicans infection prior to EAE induction in mice aggravates the disease, where a similar effect was found in MS patients [96]. Taking a closer look on the structural level, the insoluble N-acetyl-glucosamine polymer coating the fungal cell wall is usually hydrolysed by chitotriosidase ‘Chit,’ which is structurally homologous to chitinases [97]. These chitinases are synthesized and secreted by activated macrophages [98]. A study by Sotgiu S et al. revealed that the microglia-derived Chit activity in MS may protect the brain from the chitin-like substance deposition [97]. Moreover, increased Chit activity was demonstrated in the CNS of patients with different neurological disorders [98], as well as the plasma of MS patients [99]. Besides, it was reported that chitinases are increased in the CSF of patients with neuromyelitis optic in response to IL-13 thus leading to CNS inflammation through increased migration of immune cells across the blood-brain barrier [100]. Geographically, ergot fungi distribution showed a significant matching with the geographical distribution of MS [101]. Therefore, fungal infection might trigger multiple sclerosis or it may occur as a result of immune system dysfunction [102].
7. Toxicity of Chemicals, Organic Solvents and Heavy Metals

Exposure to chemicals, heavy metals and organic solvents are considered to be potential etiologic factors, contributing to the onset of MS in many studies [103], for example it was previously stated that tin, carbonic oxide and mercury but not zinc or manganese were considered to be the toxic causes of MS [104]. Areas with a high use of chemicals such as pesticides and mothballs have shown higher prevalence rates of MS [105–108]. Furthermore, workers engaged in agriculture who are exposed to pesticides, showed a higher risk of developing MS [109], particularly amongst women [110]. This could lead to an increased incidence in pregnant women and hence their babies could be more prone to MS [111]. Additionally, individuals who are subjected to chemicals such as workers in the shoe, leather and mechanical industries showed a higher risk of developing the disease [109,112]. Likewise, higher incidence of MS has been associated with areas highly polluted with heavy metals [113], such as Isfahan, the third largest city in Iran [114] and South-Western Sardinia, whereas the prevalence of MS is lower in areas of high mineral [115]. There is also a documented correlation between heavy metal imbalance and neurodegenerative pathologies [116], where toxic levels of metals when chelated from the serum led to an improvement of the MS disease status [117].

Mercury (Hg), a well-established toxicant, has been reported to be linked to autoimmunity [118] as it can induce oxidative stress as well as cause damage to DNA, mitochondria and lipid membranes [119]. Moreover, repeated exposure to mercury in animal subjects accelerated the progression of the disease through mitochondrial damage [120]. Just recently, a case of a man who injected himself with mercury provided a very good evidence that inorganic mercury is taken up by brain astrocytes, cortical oligodendrocytes, corticomotoneurons and locus coeruleus neurons. This might explain the involvement of mercury in MS and other CNS degenerative diseases [119]. Several reports have shown that the serum neuron-specific enolase (NSE-biomarker for the neurotoxic effects of mercury) is associated with the progression of multiple sclerosis [121]. Mercury-containing dental amalgam fillings increased the risk of MS [122] and was linked to neurobehavioral effects in dental personnel exposed to chronic low levels of mercury [123]. Despite these notes, data from patients with neurodegenerative diseases showed inconclusive data about a possible mercury involvement [124].

Another toxic heavy metal present in soils is lead that is associated with an increased incidence of MS, especially in males [125]. High lead toxicity and its ability to remain in the human body for prolonged time made it a suspect in the pathogenesis of many unexplained diseases [126]. The risk of MS was found to be increased 1.17 times per one µg/L increment of blood lead level [126]. However, another study stated that MS cases did not appear to cluster around lead smelters [32].

Arsenic is also present in soils and its exposure was also connected with MS disease, especially in females [125]. Consequently, arsenic may cause MS by inducing inflammation, degeneration and apoptosis of neuronal cells including hyperphosphorylation and aggregation of tau proteins leading to the deregulation of the tau function [127]. Quite the reverse, copper is used in the synthesis of myelin and hence its deficiency may potentially cause myelopathy [128]. Other metals show a controversial pattern literature such as zinc where lower serum levels were found in MS patients [129], while another study showed that zinc levels are increased in patients with MS. These results suggest that alterations of zinc concentrations may be involved in the pathogenesis of MS [130].

8. Efficacy of Various Drugs in MS Patients

For many years, several natural toxins have been described as therapeutic options for MS. Many novel compounds have been isolated from arthropods and other venomous animals for the treatment of major neurodegenerative diseases including MS [131]. These include ShK, a toxin from the sea anemone (*Stichodactyla helianthus*) and scorpion venom components, that are selective blockers of potassium channels needed for action of activated T lymphocytes [reviewed in 2]. Also, bee venom (from *Apis mellifera*) was found to ameliorate disease symptoms, improve motor function and reduce inflammatory markers [reviewed in 2]. Even snake venoms were found to play a vital role in MS therapy by inhibition of clinical signs of autoimmune encephalomyelitis and lymphocyte brain
infiltration [132,133]. New molecules derived from the venom of *Thalassophryne nattereri* Brazilian fish, so called TnP family, generate systemic and CNS specific effects that result in inhibition of inflammatory leukocyte migration to CNS and demyelination and thus could be a therapeutic opportunity for the treatment of MS [134].

Several drugs and medications have been approved to reduce MS symptoms such as glatiramer acetate, fingolimod (FTY720), mitoxantrone, IFN-β, fumaric acid esters and corticosteroids [2,135,136]. Others have been proposed to reduce MS risks, such as tetanus toxoid vaccination, antibiotics, antihistamines and antifungal agents. However, their specific role remains to be validated [31]. Tetanus toxoid vaccination was reported to reduce the risk of MS by a third in vaccinated individuals compared with no vaccination [137]. Regarding antibiotics, a correlation between penicillin use and a lower risk of multiple sclerosis was described [138]. Other medications such as antihistamines may exhibit a possible beneficial effect, if introduced during the onset of MS [139], whereas the cholesterol-lowering statins were observed to prevent and reverse chronic and relapsing EAE [140]. The anti-seizure drug valproic acid (VPA) performs its action by increasing acetylated histone levels thus resulting in increased apoptosis in the neocortex and decreased cell proliferation in ganglionic eminence [141]. Moreover, VPA assists in remyelinating the lesions in MS through the introduction of endogenous progenitors [142] and may reduce spinal cord inflammation through apoptosis in activated T cells [143]. Additionally, VPA downregulates Th1 and Th17 cells and consequently, reduce the inflammatory cytokine levels [144].

Anti-inflammatory drugs were found to affect the immune system and thus could be of therapeutic value in MS. β-Amyrin, a cannabinoid receptor agonist, reduces inflammation in microglial cells and can be used as a potential anti-inflammatory agent in the CNS especially in neurodegenerative diseases. This drug affects the inflammatory mediators profile by reducing TNF-α, IL-1β, IL-6, PGE-2, COX-2 as well as the regulation of macrophage M1/M2 balance and the differentiation of microglia [145]. Another novel agent is WWL70, an anti-inflammatory therapeutic agent, that affects microglia in EAE mouse brain by reducing COX-2 and microsomal PGE₂ expression [146]. A novel compound is JC-171 (a hydroxyl-sulphonamide analogue) that acts as a selective NLRP3 inflammasome inhibitor. In EAE mouse model, JC-171 was reported to hinder the progression and severity of the disease in both prophylactic and therapeutic experimental setups, thus encouraging its use in human MS [147]. Additionally, securinine, a major natural alkaloid product from the root of the plant *Securinega suffruticosa*, has been reported to have a potent biological activity via significant suppression of NO production in astrocytes and microglia as well as inhibition of the inflammatory mediator NF-κB and mitogen-activated protein kinases (MAPK). Therefore, it could be used as a potential therapeutic candidate for neuroinflammation related diseases [148].

Fumaric acid esters such as monomethyl fumarate (MMF) and dimethyl fumarate (DMF) have been intensively investigated over the last years. DMF has been approved for the treatment of various inflammatory mediated diseases including MS [149–151]. DMF has an immuno-modulatory function via shifting towards a Th2 cytokine profile and reducing the effect of Th1 and Th17 cells. More prominently, DMF and its metabolite MMF possess an antioxidant property by activating the nuclear factor (erythroid derived 2)-like2 (NRF2), thus stimulating cyto-protection of glial cells, oligodendrocytes and neurons [152,153]. DMF has been reported to affect the myeloid cells as well as lymphocytes including B cells and natural killer (NK) populations [154,155]. Our group investigated the effect of DMF and MMF on NK cells where we reported that they enhance the in vitro NK chemotaxis and cytolytic function [155–157]. MMF ameliorates EAE clinical score in mice by activating NK cells [42]. Fingolimod (Gilenya) also known as FTY720, a synthetic compound mimicking the fungal secondary metabolite myriocin (ISP-I), was reported to be a potent immuno-suppressant that was approved by the U.S. FDA as a therapeutic agent for MS [158]. It has been suggested that FTY720 affects the activity of immune cells such as NK cells via upregulating their activating receptors and potentiating their lytic activity against dendritic cells [159].
9. Conclusions

In this review, we shed some light on the diversity of chemicals, toxins and physical triggers in the environment that can affect the genetic and epigenetic composition of MS. These factors may modulate the function of immune players indirectly via modifying the body’s self-antigens that may be shared with CNS antigens or directly by unleashing the immune system to become unresponsive to inhibitory signals. The inconsistency of the epidemiological, experimental or clinical findings may be due to local and regional variations, both in the environment and population genetics.

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