

Review

Neuroinflammatory Markers: Key Indicators in the Pathology of Neurodegenerative Diseases

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Abstract: Neuroinflammation, a protective response of the central nervous system (CNS), is associated with the pathogenesis of neurodegenerative diseases. The CNS is composed of neurons and glial cells consisting of microglia, oligodendrocytes, and astrocytes. Entry of any foreign pathogen activates the glial cells (astrocytes and microglia) and overactivation of these cells triggers the release of various neuroinflammatory markers (NMs), such as the tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-10 (IL-10), nitric oxide (NO), and cyclooxygenase-2 (COX-2), among others. Various studies have shown the role of neuroinflammatory markers in the occurrence, diagnosis, and treatment of neurodegenerative diseases. These markers also trigger the formation of various other factors responsible for causing several neuronal diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), ischemia, and several others. This comprehensive review aims to reveal the mechanism of neuroinflammatory markers (NMs), which could cause different neurodegenerative disorders. Important NMs may represent pathophysiologic processes leading to the generation of neurodegenerative diseases. In addition, various molecular alterations related to neurodegenerative diseases are discussed. Identifying these NMs may assist in the early diagnosis and detection of therapeutic targets for treating various neurodegenerative diseases.

Keywords: astrocytes; microglia; neuroinflammation; cytokines; inflammation; neurodegenerative diseases

1. Introduction

Inflammation is a protective response against external pathogens or damaged cells. The inflammatory response is essential for the elimination of pathogens and wound healing. For years, the central nervous system (CNS) has been regarded as an immune privilege without association with inflammation. However, various new studies revealed that the

CNS shows the characteristics of inflammation when injured or infected. In this respect, CNS cells produce inflammatory mediators, such as prostaglandins and pro-inflammatory cytokines, among others, which sequentially induce the production of chemokines and adhesion molecules, recruit immune cells, and stimulate glial cells. Excessive secretion of pro-inflammatory cytokines results in neuroinflammation. The CNS is mainly composed of two types of cells: neurons and glia consisting of astrocytes, oligodendrocytes, and microglia. When glial cells are activated, which is necessary for neurogenesis (forming neurons from neural stem cells and progenitor cells), they produce cytokines. Still, overproduction of these cytokines causes different neurodegenerative diseases [1]. However, microglia participates in innate immune responses and gets activated by cellular communication and secretion via cytokines, chemokines, and other mediators [2]. Astrocytes and other neural cells communicate through neurotransmitters, which play an essential role in growth, development, and cell proliferation. On the entry of pathogens, damaged cells release adenosine triphosphate (ATP) and behave cytotoxic as a pro-inflammatory mediator. Due to the excessive release of ATP from damaged neural cells during pathology, the concentration of purine nucleotides increased. Thus, ATP may act as a chemoattractant of microglia [3].

Inflammation in the brain does not show heat, pain, redness, or swelling symptoms. This is referred to as chronic rather than acute inflammation. The key players in neuroinflammation are cellular and molecular immune constituents such as macrophages (microglia), cytokines, complement, and pattern recognition receptors [4]. In this respect, low-level neuroinflammation is protective, whereas high-level chronic neuroinflammation is harmful. Numerous factors such as trauma, the normal aging process, dementia, hypertension, stroke, depression, diabetes, drugs, and toxins, contribute to neuroinflammation in the CNS. Moreover, neuroinflammation accounts for the progression of several neurodegenerative diseases. It plays a significant part in the development of Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [5,6]. Prevalent neurodegenerative disorders are characterized by the aggregation of misfolded proteins in AD and PD. However, it does not indicate that inflammation might be the primary cause of illness. Furthermore, the pathophysiology of neurodegenerative diseases involves changes in protein conformations aggregation into neurofibrils or oligomers, which results in neuronal toxicity and ultimately leads to neuronal degeneration and brain inflammation [7–9].

Neuroinflammation is a protective physiological response in the brain that targets the CNS. It is a strong reaction that protects the brain from detrimental intrinsic and extrinsic factors; however, excess secretion of inflammatory mediators is harmful to the CNS. Neuroinflammation can be categorized into two types: neuroprotective and neurodegenerative. Neuroinflammation is neuroprotective when the effect of injury lasts for a short period. In contrast, it is neurodegenerative when it becomes chronic and lasts for an extended period with harmful effects on the CNS [4]. Inflammasomes or cytosolic molecular factories are generally composed of an adaptor protein (apoptosis-associated speck-like protein), a sensor protein, and pro-inflammatory caspase (caspase-1). The inflammasome, nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3), is the most intensively investigated inflammasome, which has been reported as a critical player in neurodegenerative diseases [10].

Cellular immune components, such as microglia or astrocytes, mediate the release of inflammatory molecules, including tumor necrosis factor, growth factors, adhesion molecules, or chemokines. Over- and under expression of pro- and anti-inflammatory molecules, respectively, may result in neuroinflammation and thus disease initiation and progression. In addition, levels of several inflammatory factors were altered in the brain or bodily fluids of patients with AD, reflecting their neuropathological changes. Therefore, simultaneous detection of several inflammatory molecules in the early or pre-symptomatic stage may improve the early diagnosis of neurodegenerative disorders [11].

In an inflammatory cascade, there is a series of immune receptors; NOD-like receptors, TLRs, nucleotide-binding oligomerization domains (NODs), microglia, and astrocytes can identify the harmful stimuli and respond by producing inflammatory cytokines such as TNF- α , IL-6, IL-1 β , Interferon- γ (IFN- γ) and several chemokines [4]. During brain development or injury, complement system components produce Toll-like receptors (TLRs) and complement receptors. These are also expressed by neuronal and glial cells. The connection linking the immune system and the CNS has been the subject of research in neuropsychiatric diseases caused by neuroinflammation [12]. In light of the importance of neuroinflammatory attributes, which are strongly associated with neurodegenerative diseases, this review focuses on these markers emphasizing the underlying mechanisms of action. In addition, the present review covers the most recent relevant literature that deals with these markers and their mechanisms of action. Presented in Table 1 are a few inflammatory molecules, their sources, and their functions.

Table 1. Inflammatory molecules and their functions [13].

Inflammatory Molecules	Family	Main Sources	Functions
IL-1 β	IL-1	Macrophages and monocytes	Pro-inflammation, proliferation, apoptosis, and differentiation
IL-4	IL-4	T-cells	Anti-inflammation, T-cell and B-cell proliferation, and B-cell differentiation
IL-6	IL-6	Macrophages, T-cells, and adipocyte	Pro-inflammation, differentiation, and cytokine production
IL-8	CXC	Macrophages, epithelial cells, and endothelial cells	Pro-inflammation, chemotaxis, and angiogenesis
IL-10	IL-10	Monocytes, T-cells, and B-cells	Anti-inflammation and inhibition of the pro-inflammatory cytokines
IL-12	IL-12	Dendritic cells, macrophages, and neutrophils	Pro-inflammation, cell differentiation, and activation of NK cells
IL-11	IL-6	Fibroblasts, neurons, and epithelial cells	Anti-inflammation, differentiation, and induces acute phase protein
TNF- α	TNF	Macrophages, NK cells, CD4 ⁺ lymphocytes, and adipocyte	Pro-inflammation, cytokine production, cell proliferation, apoptosis, and anti-infection
IFN- γ	INF	T-cells, NK cells, and NKT cells	Pro-inflammation, innate, and adaptive immunity anti-viral
GM-CSF	IL-4	T-cells, macrophages, and fibroblasts	Pro-inflammation, macrophage activation, increases neutrophil and monocyte function
TGF- β	TGF	Macrophages and T-cells	Anti-inflammation and inhibition of pro-inflammatory cytokine production

2. Neuroinflammatory Markers in the Pathogenesis of Neurodegenerative Diseases

2.1. Tumor Necrosis Factor- α (TNF- α)

In the brain, TNF- α , a pro-inflammatory cytokine, is mainly produced by neurons and glial cells, including astrocytes and microglia as the significant glial cells [14]. By initiating inflammatory cytokine signaling cascades, TNF- α plays a vital role as a regulator of acute phase inflammation, acting as a key player in inflammation [15]. Besides injury and inflammation, TNF- α is also responsible for various physiological functions, including fetal development, hematopoietic cell regeneration, cardiovascular health, and different immune system constituents [16,17]. In addition, TNF- α maintains the maturation of dendritic cells, establishes a synaptic connection, responds to various changes in sensory stimuli, and retains homeostatic flexibility [18,19]. Furthermore, TNF- α is the critical regulator of α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors synchronized signaling. Notably, glial TNF- α improves synaptic efficiency by increasing the cell-surface appearance of AMPA receptors. On the contrary, jamming of TNF- α -directed signaling has a contradictory action [20].

At the onset of injury, TNF- α provides protection against infection, neuronal degeneration, and neuronal toxicity. However, uncontrolled TNF- α expression leads to chronic inflammation, high gliosis, synaptic loss, and glutamatergic toxicity. Persistent expression of TNF- α is detected in multiple sclerosis (MS), HIV-associated dementia, Parkinson's disease (PD), ischemia, and Alzheimer's disease (AD) [21,22]. An increase in brain TNF- α plays a role in the pathogenesis of neurodegenerative disorders. In this respect, for any delayed inflammatory response that will result in malfunction, TNF- α may be a principal remedial target as a treatment approach to diminish neurodegenerative diseases [23].

2.2. Interleukin-1 β (IL-1 β)

In the pathology of neurodegenerative diseases, interleukin (IL)-1 is an essential inflammatory cytokine, which acts as a significant key molecule in MS [24]. Levesque and co-workers reported that neutrophils and monocyte-derived macrophages express IL-1 β in experimental autoimmune encephalomyelitis (EAE), leading to their transmigration into the spinal cord parenchyma [25]. Microglia and astrocytes are the two key players in neuroinflammation that respond to IL-1 β [26,27].

Research findings showed that IL-1 β induces a quick pro-inflammatory reaction in the cell culture of astrocytes, leading to the cytokine's expression and adhesion molecules, chemokines, and matrix metalloproteinases [28,29]. IL-1 also plays a role in neurodegeneration, induces IL-6 production, and stimulates inducible nitric oxide (iNOS) activity in astrocytes [30]. Additionally, IL-1 enhances brain acetylcholinesterase activity and microglial activation. In this respect, more IL-1 production results in astrocyte activation, and expression of the beta-subunit of the S100 protein (S100 β) by astrocytes, thus establishing a self-processing cycle [31,32]. Interleukin-6 (IL-6) performs various roles in neuroinflammation and is one of the key roles in defending the host [33] with focused regulatory effects leading to the inflammatory response [34]. IL-6 is also associated with the neuropoietic family of cytokines [35] and exerts direct and indirect neurotrophic effects on neurons [36]. IL-6 stimulates astrogliosis microglial activation and boosts the production of acute-phase proteins [37,38].

2.3. Nitric Oxide (NO)

Nitric oxide (NO), a small bioactive lipophilic molecule that diffuses crossways to the cell membrane, controls numerous physiological functions of the body [39]. NO production occurs in the presence of nitric oxide synthase (NOS), which catalyzes L-arginine oxidation to L-citrulline [40]. There are three different isoforms of NOS found in mammals: inducible NOS (iNOS), endothelial NOS (eNOS), and neuronal NOS (nNOS) [41]. The eNOS and nNOS collectively accomplish the vasodilation of vessels and functions of the CNS. In addition, numerous inflammatory triggers can induce the iNOS expression in different types of cells, such as neutrophils, macrophages, dendritic cells, and epithelial cells [42]. iNOS is also expressed in endothelial cells at the blood-brain barrier (BBB), microglial cells, astrocytes, and neurons in the brain [43]. Published research showed a medical connection between iNOS and the pathogenesis of organ-specific autoimmune inflammatory diseases, MS, and experimental autoimmune encephalomyelitis (EAE) [44,45]. The iNOS expression in microglial cells and macrophages results in high levels of NO and peroxynitrite, which ultimately causes damage to the CNS [46].

2.4. COX-2

Cyclooxygenases (COX) are enzymes that convert arachidonic acid into prostanoids. Three isoforms of COX have been described: COX-1, 2, and 3; COX-1 and COX-2 isoforms are involved in neurodegenerative diseases. COX-2 is stimulated by inflammatory components such as cytokines, TNF- α , IL-1, and IL-2 and has been documented for its combined expression in some cell masses of the brain [47]. Studies reported that COX-2 expression is deficient in astrocytes [48], increases in the early phases of the disease [47,48], and is principally expressed in pyramidal neurons [49].

2.5. Reactive Oxygen Species (ROS)

ROS cause a damaging effect on neurons and accumulate in the brain, resulting in neurodegenerative diseases [50]. In addition, ROS can cause damage to macromolecules such as proteins and lipids, which obstruct mitochondrial functions. ROS damage lipids by interrupting lipid peroxidation to malondialdehyde (MDA), protein carbonyls, and guanine oxidation to 8-oxo-deoxyguanosine in DNA [50,51]. ROS also disrupt the mitochondrial DNA, which is linked with decreased mitochondrial gene expression.

3. Role of Neuroinflammatory Markers in Neurodegenerative Diseases

3.1. Alzheimer's Disease

Recent studies have revealed the significant role of neuroinflammation in the progression of the neuropathological alterations in Alzheimer's disease (AD). Researchers have shown the relationship between immune-linked proteins and cells near the plaques of β -amyloid [32,52]. At the beginning of the 1990s, several findings emphasized the vital function of neuroinflammation in AD progression. In this respect, the protective properties of anti-inflammatory drugs against various disorders, including rheumatoid arthritis, and AD development have been reported in multiple studies. Those studies showed that people taking non-steroidal anti-inflammatory drugs (NSAIDs) for a long time have decreased the risk of developing AD [53–55]. Similarly, several studies have demonstrated the importance of inflammatory processes in AD development. However, the inflammation hypothesis linked to AD pathogenesis has been recently proposed. Even in this hypothesis, the inflammatory reaction is believed to be a consequence of tau and β -amyloid protein [56,57]. Inflammation of the brain seems to display a dual function by showing a neuroprotective effect in the acute-phase stimulus; however, it appears to be harmful when a chronic stimulus is activated [58]. The stimulation of microglia via traditional means leads to the release of different pro-inflammatory and detrimental molecules such as NO, ROS, and cytokines. Furthermore, increased levels of interleukin 1 β enhance the formation of other cytokines such as interleukin 6, which then activates CDK5 stimulation, a kinase known to induce tau hyperphosphorylation. The neuroinflammation in AD plays a significant role in increasing the burden of A β and hyperphosphorylation of tau, indicating that this dual function could be a major bound between the pathologies of AD. Stimulation of the resident macrophage of the brain is now a primary factor in the investigation of AD [52,59].

3.1.1. Microglial and Alzheimer's Disease

Microglia are the primary immune cells in the central nervous system. In a normal brain, microglia are 'resting' and are structurally ramified cells with somas [60,61]. In this context, the cell somas do not move, whereas the cell processes extend and retract, monitoring their environment and interacting with nerve cells and other glia cells. When microglia detect a condition in the CNS, such as injury, invasion, or disease, it results in microglial stimulation, leading to a morphological alteration, which causes cell enlargement, retraction of processes, and migration [62–64]. In AD, studies showed that the primary factor of the microglia stimulation is the presence of A β . In the early stage of AD pathogenesis, the stimulated immune stimulus leads to A β clearance and displays positive action on pathologies linked to AD in animal studies [53,65]. However, A β accumulation and sustained pro-inflammatory cytokine initiation induce nerve cell damage [66,67]. Additionally, the sustained microglial activation leads to a reduction in the efficiency of microglia responsible for interacting and phagocytosing A β and a drop in the activity of A β degrading enzyme, resulting in a decreased ability to degrade the plaques of A β . At the same time, it was observed that the capacity of microglia to form pro-inflammatory cytokines is not altered [68,69]. Furthermore, findings showed a specific property of pathogenesis in which the total clearance of A β becomes affected. The continuous formation of neurotoxins from microglia leads to an increase in neuroinflammation and neurodegeneration, resulting in excessive activation of microglia [52].

The involvement of microglia in A β clearance induces the formation of pro-inflammatory cytokines that stimulate the release of more microglia to plaques [11,70,71]. Recent studies showed that low clearance of A β by microglia induces macrophages from the deposition of A β plaque to clear A β [72]. In this regard, peripheral macrophage recruitment into the brain may cause the influence of sustained inflammation and, therefore, AD pathology. Most recent studies regarding the role of inflammation in the pathogenesis of AD and control of immune response indicated that an alteration (mutation) in the triggering receptor expressed on myeloid cells 2 (TREM2) has a greater possibility of causing AD [72–74]. An uncommon missense mutation substantially exacerbated AD risk [75].

3.1.2. The Pathology of Alzheimer's Disease and the Role of TREM2

Recent works on genetic variations of TREM2 have emphasized the interest in the mechanisms implicated in AD pathogenesis and several other neurodegenerative disorders [52]. Initially, the interest in the role of neurodegeneration and TREM2 started in the 2000s when links were discovered between TREM2 and Nasu-Hakola disease and polycystic lipomembranous osteodysplasia with sclerosing [76,77].

3.1.3. Cross Talk between Peripheral and CNS Immune Cells in Alzheimer's Disease

Activation of microglia and astrocytes leads to the release of soluble inflammatory mediators that, instead of staying in the local vicinity, can cross the blood brain barrier (BBB), inflammatory mediators then disperse into the bloodstream and move around the periphery. Simultaneously, the CNS is solely responsible for the activation of the immune system; on the onset of injury/pathogen attack, pro-inflammatory cytokines released by peripheral cells travel through blood flow towards the BBB. When cytokines cross the brain parenchyma they act upon glial cells, responsible for increasing their vulnerability to disease [78,79]. There is an increase in inflammatory signals in the brain, which can activate resident immune cells and convert them to a pro-inflammatory phenotype [80].

3.1.4. Progression of Mild Cognitive Impairment to Alzheimer's Disease

Criteria for a dementia syndrome and probable AD were [81] designed to be conservative so that a neurodegenerative condition could not be established unless the cognitive function was sufficiently compromised to interfere with either an individual's social, occupational, or both, functions. Because AD develops several years before cognitive symptoms arise, cognitive deficits appear before the onset of a full-blown dementia syndrome [82], and more emphasis is being paid to mild cognitive impairment (MCI) as a stage between normal cognition and AD [83]. The presence of a memory or other cognitive complaints by an individual or other knowledgeable informants, objective deficits on standardized objective cognitive tests, and the absence of a dementia syndrome characterized by intact general intellectual function and no significant deficits in either social, occupational, or both, functions is the generally accepted criteria for MCI. As disease-modifying drugs are identified, the best hope for prevention or cure is to treat the problem early on, before multisystem degeneration significantly compromises the brain [84,85].

3.2. Parkinson's Disease

After the inflammatory pathway stimulation by defective signals, there is an impairment synapse by many molecular mechanistic actions. This process also leads to a positive feedback loop that contributes to more significant injury, which is regulated by microglia cells [86]. In this regard, elevated blood-brain barrier permeability and neurovascular impairment could be associated with inflammation molecules infiltration into the middle brain, dopaminergic nerve cell death, and activation of microglia. The inflammatory stimulus in PD appears to be improved by activation of peripheral lymphocytes, and augmented concentrations of serum mediators including IL-6, IL-2, and TNF- α are observed in PD patients [87]. However, there is no confirmation of pro-inflammatory mediator's secretion linked to PD [88]. Among the several mechanistic pathways, which move cells of the

immune system and microorganisms into the brain, are direct vascular channels. These channels link the bone marrow in the skull to the brain's surface via the meninges, making other cells move into this part, usually regarded as 'aseptic' [89]. Leukocytes formed from the bone marrow can stimulate inflammatory processes in the tissue and display their protective action [88].

Moreover, numerous brain pathologies, which contribute to neurodegeneration, show neuroimmune dynamics stimulating neuroinflammation, apart from their other mechanistic actions [86]. Pathogens and inflammatory processes, which enable the immune stimulus contribute to the progression and initiation of PD and several other neuronal disorders following their invasion of brain cells [88]. The previous sections showed that microglial activation can be enhanced by various impaired signals such as toxins, pathogens, molecules formed by dying nerve cells, endogenous proteins, and other toxic molecules. Furthermore, the expression of constitutive pro-inflammatory mediators such as TNF- α , IL-6, IFN- γ , IL-2, IL-1 β , eicosanoids, and ROS were observed in post-mortem PD patients. The microglial stimulation may result in a vicious circle of neurodegeneration and neuroinflammation [87,88]. In recent studies, astrocytes have been involved in α -syn fibrils degeneration. This mechanical action is stimulated by α -syn transfer to surrounding cells, which are more effective in astrocytes and are found inside lysosomes, where they appear to be broken down [88,90]. After that, it was documented that α -syn fibrils move via tunneling nanotubes between nerve cells inside lysosomes and stimulate the aggregation/misfolding of the standard proteins since lysosomal impairment is a significant factor in neurological diseases [91].

3.3. Amyotrophic Lateral Sclerosis

Neuroinflammation, characterized by astrocyte and microglial activation, infiltration of T lymphocyte, and inflammatory cytokines overproduction, has been linked with neuronal loss in both human and animal tissues in the amyotrophic lateral sclerosis (ALS) pre-symptomatic phase [92]. Findings from a preclinical study have implicated immune system cells in either displaying protective or harmful actions on motor neurons (MN) survival, depending on the point of disorder progression. However, the mechanism is still speculative [93].

3.3.1. Microglia and Amyotrophic Lateral Sclerosis

Microglia are the main form of active defense activities of the immune system in the spinal cord and brain. They monitor the brain's environment and respond to 'harmful signals' resulting from damaged or injured tissues. Published research showed that damaged astrocytes and MNs liberate misfolded proteins, including human mutant superoxide dismutase 1 (mSOD1) in ALS, which stimulates microglia via Toll-like receptor (TLR) 2, CD14, TLR4, and scavenger receptor-dependent cascade [94–96]. Direct evidence of microglia activation in the brain of individuals with ALS and mice with SOD1^{G93A} was determined with the help of positron emission tomography [97–99], with a marked correlation between microbial stimulation intensity in the motor cortex and the potency of MN impairments [99]. A study on mSOD1 transgenic mice showed that the substitution of mSOD1 microglia with wild-type microglia and that the decreased expression of mSOD1 in microglia blocks the degeneration of MN and prolongs the animal's life span [100,101]. Similarly, the work of O'Rourke and co-workers showed that the expression of C9orf72 was highest in myeloid cells and that blocking the activity of C9orf72 in experimental mice induces impairments in lysosomal trafficking, reduces microglia's ability to remove aggregated proteins, and causes neuroinflammation and alters microglia stimuli [102]. Concomitant results in macrophages showed that even C9orf72 haploinsufficiency promotes impaired inflammatory stimuli in macrophages. These results indicate that C9orf72 may have a dual effect on myeloid and nerve cells [93].

On the other hand, ATP liberated by impaired nerve cells may stimulate microglia via the metabotropic P2Y and ionotropic P2X purinergic receptors. In this context, findings

indicated that the level of P2X₇ expression increases in microglia of the post-mortem spinal cord of patients with ALS [103]; a similar situation is observed in SOD1^{G93A} mice [104]. In addition, it was found that up-regulation of P2Y₆, P2X₇, and P2X₄ receptors in mSOD1 microglia, is associated with decreased hydrolysis of ATP in the same microglial ALS, which induces elevated synthesis of cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF- α) with consequent toxic effect to neurons [105]. Other studies have shown the harmful effect mediated by microglia in ALS could be blocked by genetic impairment of P2X₇ receptors or by utilizing specific receptor antagonists [104,106]. However, other studies showed the role of multiplex P2X₇ in the pathogenesis of ALS. In this respect, Apolloni and co-workers discovered that constitutive deletion of the P2X₇ receptor contributes to the progression of the disease, elevated astrogliosis, loss of motoneuron and microgliosis, stimulated MAPKs cascade, and exacerbated the liberation of pro-inflammatory markers including iNOS and nicotinamide adenine dinucleotide phosphate oxidase 2 in the end-stage lumbar spinal cord in SOD1^{G93A} mice [107]. In addition, findings showed that administration of P2X₇ antagonist at the beginning of the pre-symptomatic phase (Brilliant Blue G) remarkably promoted the survival of MN in the lumbar spinal cord via decreasing microgliosis and control inflammatory markers expression [108].

Published data highlight the dual activity of P2X. The double-action of P2X₇ during the progression of ALS may be associated with the switch of microglia from the protective M2 to harmful M1 phenotype. Thus, the advance of ablation of the receptor is harmful, and its therapeutic blockade at the initial pre-symptomatic stage or after the onset of the disease might be too late or too early. Stimulated microglia showed specific and flexible phenotypes, with either neuroprotective or neurotoxic action, depending on activation stage and disease state. In the early ALS progressive stage, microglia show a phenotype with up-regulated M2 markers expression including Ym1 and CD206, which contribute to tissue regeneration and repair and react with protective signals including fractalkine and CD200 [94,109]. As the disorder progresses, damaged MNs liberate 'harmful signals' such as mSOD1 that cause microglia to possess the M1 phenotype with the marked formation of ROS, NADPH oxidase 2 (NOX2), and pro-inflammatory cytokines such as interleukin-6 (IL-6), TNF- α , IL-1 [101,110]. An in-vitro study reported that, at the early stage of M2, microglia improved the survival of MN, whereas, at the end-stage of M1, microglia were harmful to MNs [110].

3.3.2. Astrocytes and Amyotrophic Lateral Sclerosis

Genes associated with ALS are expressed in astrocytes and their expression in MNs [111,112]. In-vivo and in-vitro studies showed that astrocytes with mSOD1 expression are harmful to both MNs, formed from embryonic stem cells (ESC) with mSOD1 gene and normal MNs [113,114]. Selective blockage or silencing of the gene for mSOD1 gene in astrocytes or healthy astrocytes transplantation could lessen the loss of MN and astrocyte-mediated toxicity and delayed mSOD1 mice lifespan [115–117]. On the other hand, it is reported that transplantation of astrocytes with mSOD1 caused death and degeneration of focal MN in wild-type rats' spinal cords [118]. Additionally, astrocytes formed from ALS individual fibroblasts affect the MNs survival and therefore, the expression of mutant proteins linked to ALS in astrocytes leads to non-cell-autonomous toxicity. Qian and co-workers discovered that non-MNs were lost before MNs, indicating ALS astrocytes-induced non-cell-autonomous toxicity and showing that sporadic ALS astrocytes can induce neuronal degeneration [119].

As stated above, astrocytes are vital in ALS; however, it is still speculative how mutant proteins linked to ALS lead to astrocytes impairment and how impaired astrocytes display toxicity that is non-cell-autonomous to MNs. Astrocytes attenuate excess glutamic acid from synaptic clefts via glutamic acid transporters. In familial and sporadic individuals with ALS and mice models with mSOD1, loss of glutamic acid transporters (EAAT2/GLT-1) caused a decline in glutamic acid uptake by astrocytes. It thus increased the degeneration of MN [93,119,120].

Mitochondrial impairments in mSOD1 (not in wild-type astrocytes) are harmful to MNs, and this could be blocked by inhibitors of nitric NOS and antioxidants [121,122].

Moreover, post-mortem-derived astrocytes with ALS conditions and mice with SOD1^{G93A} display harmful actions on MNs by releasing inflammatory markers such as leukotriene B4 and NOX2, prostaglandin E2, and NO [122,123]. A recent report showed that astrocytes contribute to the death of MN by stimulating a caspase-independent type of apoptosis known as necroptosis, which involves plasma membrane integrity loss via receptor-interacting mixed lineage kinase domain-like and threonine/serine-protein kinase 1. Abrogation of the major necroptosis effectors (mixed lineage kinase domain-like or threonine/serine-protein kinase 1) could confer protection of MNs against toxicity of non-directional ALS astroglia and prolong the initiation of motor impairment, thus indicating these as possible novel therapeutic targets [124,125].

3.4. Huntington Disease

Huntington's disease (HD) is a devastating autosomal dominant neurological disorder characterized by emotional impairments, loss of weight, motor impairment, and dementia [126]. The first gene responsible for the disorder was cloned in 1993, and its codes for a highly conserved protein with unknown actin is called huntingtin (htt) [126,127]. In persons with HD, a polymorphic trinucleotide repeat sequence, CAG_n, at the gene 5' end is enlarged more than the standard repeat limit, resulting in the translation of an enlarged series of polyglutamine in the protein [126]. Mutant 'htt' proteolytic cleavage is vital in HD pathogenesis [128,129]. These abnormal 'htt' fragments stimulated a complicated pathway of compensatory and damaging molecular processes, such as neuroinflammation. These processes result in marked atrophic, fragile, impaired nerve cells susceptible to different stressors, including excitotoxic stress, oxidative damage, pro-apoptotic signals, depletion of energy, impaired proteolysis, and defective neurophysiology. All these might be involved in the death of neurons [129].

Microglia and Huntington's Disease

Apart from other CNS disorders, microglia's role in HD is not yet fully explored [130]. Singhrao et al. were the first to document the impairment of microglia in individuals with HD [131]. The number of microglial cell counts is elevated in the HD caudate-putamen, and their expression promoted the number of complement factors. Later on, a more comprehensive study on microglial morphological alterations linked to HD was carried out by Sapp and co-workers [132]. Their work localized structurally stimulated microglial cells in the cortex, globus pallidus, and neostriatum. In the cortex and striatum, the collection of thymosin β -4 reactive microglia was elevated with levels of pathology. In another study, accumulation of microglia was observed in HD tissue and the striatum R6/2 mouse model [130,133]. Furthermore, this report was the first to indicate that microglial express htt^{exp}, which in specific cells form aggregates. It has been shown that accumulated htt^{exp} induces transcriptional alterations in nerve cells and that microglial transcription might be similarly affected [130].

Silvestroni and co-workers showed that post-mortem tissue of human HD has a clear inflammatory effector profile [134]. Inflammatory molecules such as TNF- α and IL-1 β , were specifically elevated in the striatum, whereas MMP-9, IL-6, and IL-8 were up-regulated in the cortex and cerebellum region [130]. This is different from the other known neuroinflammatory indices of the other neurodegenerative disorders such as PD or AD, which indicate an up-regulation of a broad category of inflammatory molecules [135,136]. It is assumed that the inflammatory regulators seen in the striatum are indications of the ongoing pathological processes. At the same time, the abnormal regulation of molecules such as MMP-9, IL-6, and IL-8, indicate the more generalized effect of htt^{exp}. In addition, researchers have shown that IL-6 secretion is elevated in htt^{exp} expressing monocytes in human HD. Based on the preceding discussion, it will be safe to say that HD, in contrast to other neurological disorders, including AD and multiple sclerosis, peripheral immune

cells influx, including neutrophils or lymphocytes, has not been fully covered. Moreover, it was reported that T-cells are not elevated in the post-mortem tissue of human HD [134]. Thus, HD neuroinflammation appears mainly sustained by the interactions of nerve cells, microglia, and macrophages [130].

3.5. Prion Disease

Initially, it was presumed that prion disease (PRD) does not stimulate the immune system due to the lack of a humoral stimulus to protease-resistant prion protein and interferon formation in the infected organism [137]. Later, it was found that an assortment of pro-inflammatory chemokines and cytokines are elevated in the CNS in response to prion infection. The neuroinflammation may be caused by CNS cells because leucocyte infiltration from the periphery has a limit and are mildly detectable mainly at the end phase of the disease [138,139]. Many high-throughput procedures, including suspension array systems and microarray expression profiling, have shown protein transcriptional changes in the brains of prion-infected mice compared to the controls. It is now known that PRD has a neuroinflammatory component that is involved in neurodegeneration, with elevation in several pro-inflammatory chemokines and cytokines, such as TNF, IL-1 α , IL- β , CXCL10, and CCL2-CCL6, in the brain of infected mice [138,140,141]. The qRT-PCR array, is a more focused and sensitive strategy, which gives room for estimating temporal alterations in several genes by comparing scrapie strains 22L-infected mice at 131, 94, 70, and 44 dpi with mock-challenged mice. In this respect, various pro-inflammatory cytokines are elevated at 44 dpi, and the quantity increases as prion disorder progresses. It seems that neuroinflammation during prion disorder increases with time, resulting in severe inflammation that may promote the pathogenesis of prion [138,140].

Many of the proteins/genes appear to be chronically elevated during scrapie infection, possibly harmful to the host's CNS. Expression of *Ccl5*, *Iasa1*, *Olr1*, *Oas1a*, and *Tnfsf11* is linked to the stimulation of cellular apoptosis [142–144], whereas the expression of *Tnf*, *Cxcl10*, *A2m*, and *Ccl1* promote neurotoxicity in other models of the disease [145–148], indicating that signal transduction via these pro-inflammatory molecules and their receptors can result in injury. Research findings showed that several mouse-adapted scrapie cause similar profiles of elevated inflammatory proteins and genes [149]. In this respect, an aqRT-PCR study involving ten signaling cascades showed that the NF- κ B and JAK-STAT are substantially stimulated in mice with prion disease. More than 50% of the pro-inflammatory genes were elevated in prion disorder, which NF- κ B could boost. Moreover, numerous additional genes marked are mediated by specific STAT complexes [149]. Phosphorylated STAT3 and STAT1 are elevated in scrapie strain ME7 mice. Consistently, it was shown that in 22L-scrapie there is an elevation in overall STAT1 α and pSTAT3 and pSTAT1 α [149].

On the other hand, phosphorylated STAT proteins are involved in synergistic action with NF- κ B, which might occur in PRD. NF- κ B and pSTAT3 have been reported to affect transcription at the promoters regulating genes that are elevated in the CNS during prion infection (that is, *A2m*, *Ccl4*, and *Cxcl10*) [150–152], and together they potentially affect acute-phase protein expression, including ceruloplasmin, serum amyloid A, haptoglobin, and α 1-anti chymotrypsin [153–155]. In addition, regions of the NF- κ B complex, such as RELA, can bind with STAT3 to change transcriptional action [156–158]. Moreover, there have been multiple reports describing the expression of several inflammatory genes such as *Icam1*, *Ccl5*, *Nos2*, and *Cxcl9*, by STAT1 and NF- κ Bh, which also show an elevation in scrapie disease [159,160]. Though many signaling cascades promote neuroinflammation in the brain with prion infection, the actual cause of the cascade activation is still speculative [161].

Several studies have investigated mice lacking immune genes such as *Tnfr1*, *Ccr2*, *Tnf*, *Cxcr5*, IL-6, and *Ccr5*, and showed that expression loss of these genes does not affect the pathogenesis of prion [161–163]. Removing some genes, such as *IL-10* and *Ccl2* [162,164,165], on prion infection has proven controversial by both reducing and prolonging survival times in mice. In addition, *IL1r1* deletion extended the incubation time in infected mice; however, the incubation time of mice with prion infection is reduced and

lacks the expression of *IL-13*, *IL-4*, *Cxcr3*, *Tlr2*, and *Tlr4* [164,166,167]. Although removing many immune effectors does not change the pathogenesis of prion, it is vital to know that the disease is still fatal and progressive. Another overlapping or intact system may replace immune molecules. Therefore, it is not new that applying single deletion mutation may result in partial prevention from prion disease. Accordingly, different strategies including network analysis to alter and identify ‘signaling bottlenecks’ may be required to understand the neuroinflammatory role in the pathogenesis of prion infection [161].

Researchers have shown that statins reduce inflammation in different neurodegenerative disorder models [168,169]. Simvastatin and atorvastatin affect neuroinflammation in PD mouse models by decreasing brain pro-inflammatory proteins. In addition, atorvastatin decreases pro-inflammatory cytokine production and lessens microglia number in the hippocampus in AD rodent models [170,171]. In a similar work, statins decreased pro-inflammatory cytokines and monocytes infiltration into the CNS, elevated anti-inflammatory stimuli, and reduced the expression of adhesion molecules on cells of the immune system in rodents with experimental autoimmune encephalomyelitis for multiple sclerosis [172–174]. Furthermore, certain clinical studies showed that statin intervention decreases PD incidence. However, other studies revealed that the drugs are inefficacious in inhibiting risk, progression, or linked dementia in PD [175–177]. Mixed findings have also been reported in human studies investigating the efficacy of statins on AD progression. Some studies showed that statin intervention improved memory and enhanced cognition in individuals with AD [168,178,179]; however, other works revealed no effect of the statin intervention [168,176,180]. Moreover, studies involving human subjects with multiple sclerosis showed that treatment with statins might provide little beneficial effect [161,181–183].

4. Glial Cells and Neuroinflammatory Markers

4.1. Microglial

Microglia are the brain’s primary innate immune cells and the first to react to pathological injuries [184,185]. They have three crucial roles in maintaining homeostasis and defending the host [186]. They first detect changes in their surroundings via their sensomes, encoded by multiple genes [186]. Their second function is physiological housekeeping, which includes migration to injured sites, synaptic re-modeling, and myelin homeostasis [187,188]. The third phase protects against damaging stimuli such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Toll-like receptors (TLRs), nuclear oligomerization domain-like receptors, and viral receptors are among the cellular receptors that microglia express to recognize PAMPs and DAMPs [189,190]. Microglia release pro-inflammatory cytokines such as TNF, interleukin (IL)-1, IL-16, and chemokines such as C-C motif chemokine ligand 2 (CCL2) and IL-18 in response to such stimuli recruiting additional cells and eradicating harmful chemicals [186,189]. Despite its beneficial properties, neuroinflammation can also produce neurotoxicity and is associated with neurodegeneration [186]. Furthermore, microglia priming causes dystrophic morphology and enhances inflammatory response in the context of aging and chronic stress [191]. Microglial activity can be measured via imaging and fluid markers. In addition, 11C-(R) PK11195 positron emission tomography (PET) can be used to detect microglial activation because of its ability to bind to the translocator protein that is overexpressed in activated microglia [192,193]. The microglial activation biomarker sTREM2 (soluble triggering receptor expressed on myeloid cells 2) is a fluid biomarker. It is a TREM2 cleavage product expressed on microglia cell surfaces [194,195]. Recent research has discovered a relationship between CSF sTREM2 levels and plasma sTREM2 levels, implying that CSF sTREM2 could be a biomarker for microglial activation [195,196].

Inflammatory responses play a beneficial role when stimulated in a well-regulated way for a definite time; though, extended or disproportionate dysregulated inflammation causes several systemic, chronic diseases such as multiple sclerosis, arthritis, and systemic lupus erythematosus, and many more [197]. In adaptive immune responses, these cells are

chief players, that obstruct viral increase during the cytotoxic reaction, with other related inflammatory actions. It was reported that remaining T lymphocytes have been identified inside the postmortem brain tissue after viral infection which led to the study of T-cell: microglial cell interactions [198].

4.2. Astrocytes

Astrocytes are the most common glial cells in the brain [199]. Although astrocytes were previously assumed to have passive roles, new research revealed that they play an active and critical role in maintaining brain homeostasis [200]. They regulate the extracellular balance of ions, fluid, transmitters, and scar formation, by keeping the BBB, delivering energy metabolites to neurons, influencing synaptic activity, governing neurotrophin production, eliminating dead cells, and maintaining the BBB [199–201]. GFAP, S100B, YKL040, and D-serine are now being investigated as CSF biomarkers, whereas GFAP and S100B are blood biomarkers [202]. In imaging biomarkers, astrocyte reactivity is measured by magnetic resonance spectroscopy, ¹¹C-deuterium-L-deprenyl (¹¹C-DED) PET, and ¹¹C-BU PET [202]. The degree of reactive astrogliosis, a hallmark of CNS illness, can be determined by GFAP, which measures astrocyte molecular expression and morphology [201].

According to a study in a chronic experimental EAE mouse, astrocyte defects are consistently linked to worsened clinical outcomes, neuroinflammation, BBB alteration, and neuronal death during the early stages of injury, such as spinal cord injury (SCI) and experimental autoimmune encephalomyelitis (EAE) [199]. Astrocytes produce lactosylceramide (LacCer) during chronic CNS inflammation, promoting inflammation and neurodegeneration. These data imply that the effect of astrogliosis may be advantageous or harmful depending on the time, disease, and other inputs from the microenvironment, such as microglia. Moreover, astrocytes have a continuous spectrum and can have multiple response profiles simultaneously. As a result, more significant research into reactive astrocyte heterogeneity is required [203]. Similarly, astrocytes have pro-inflammatory and immunoregulatory (neuroprotective) subpopulations. Pro-inflammatory reactive astrocytes up-regulate a variety of genes (e.g., complement cascade genes) and create pro-inflammatory chemicals (e.g., IL-1, TNF-, and NO), all of which have detrimental consequences [189,204]. On the other hand, neuroprotective reactive astrocytes up-regulate numerous neurotrophic factors, including thrombospondins [204]. Anti-inflammatory cytokines such as IL-4, IL-13, and IL-10 can activate astrocytes and cause them to produce IL-4, IL-10, and TGF [200,205].

4.3. Oligodendrocytes

In neurodegenerative disorders, oligodendrocyte death and myelin loss may directly respond to cytotoxic viral infections such as the JC virus, which causes progressive multifocal leukoencephalopathy [206]. The immune response is focused on the virus and infected cells that are undergoing apoptosis and necrosis in these circumstances. Cells attacked by viruses or exposed to ROS begin stress response pathways to fight and prevent damage and apoptosis. Numerous mechanisms are known to generate oligodendrocyte stress, including several pathophysiological events, such as inflammation, genetic abnormalities, mitochondrial malfunction, hypoactive N-methyl-d-aspartate receptors, and neuronal and axonal damage. The myelin-producing cell, as previously stated, is susceptible to oxidative stress. Pro-apoptotic signaling cascades are triggered when the sphingomyelinase/ceramide pathway is activated, leading to oligodendrocyte loss in pathological circumstances such as ischemia and MS [207].

Furthermore, research findings showed that metabolic abnormalities such as unbalanced glucocorticoid levels reduce oligodendrocyte proliferation and viability. It has been claimed that oligodendrocyte abnormalities in depression are caused by such modifications [208]. The myelin-producing cell is prone to glutamate toxicity and pro-inflammatory cytokines, which are essential players in brain injury, due to the expression of a variety of receptors. One of the most prominent factors of oligodendrocyte stress is inflammation. Studies suggest that pro-inflammatory cytokines have the potential to impair

the oligodendrocyte as early as development. In an in-vivo study, LPS is induced on the 15th-day pregnant mouse, and it is observed that apoptosis of oligodendrocytes occurs after five days from an injection, and hypomyelination occurs on the 21st day after birth [209]. Besides the damaging effect of pro-inflammatory cytokines released during these infections, the accumulation of pathogens also leads to the destruction of the cell [207,210]. In humans, maternal infection with the herpes simplex virus, the chance of the offspring developing neuropsychiatric illnesses are linked to oligodendrocyte abnormalities including autism and schizophrenia [208,209].

Tumor necrosis factors are cytokines, produced by glia, neurons, and macrophages, and established as key regulators of several immune processes. They act as pro-inflammatory factors, induce gene expression and apoptosis, serve as gliotransmitters, and regulate synaptic communication between cells [211,212]. In contrast, the growth factors in the CNS and peripheral nervous system play a role in brain development and axonal growth. They also support the growth and survival of nerve cells and play mostly a protective role in the different neurological disorders, including AD [38].

Chemokines are expressed in every cell type of the CNS. While some chemokines (e.g., CXCL13 and CX3CL1) are found in normally functioning brain cells and play a role in typical intercellular communication, others are up-regulated after a brain injury. In fact, both acute and chronic inflammatory reactions can result in the up-regulation of chemokines and chemokine receptors. Chemokines play multiple roles in AD progression; they might be involved in inflammatory processes and also in neuronal survival [213–215]. Meanwhile, cell adhesion molecules (CAMs) mediate the interaction between immune cells and the surrounding environment, such as helping the monocytes migrate through the BBB. CAMs play roles in cell survival, activation, and migration [216].

4.4. Blood-Brain Barrier (BBB) Proteins in Neurodegenerative Diseases

Glial cells are one of the most important components of the BBB, which is a continuous membranous network that surrounds the arteries and organizes molecular signals via pericytes and ECs. This 'highly selective permeability barrier' keeps brain homeostasis in check by allowing essential nutrients into the CNS while keeping potentially hazardous chemicals out [217,218]. As a result, the BBB plays a crucial role in protecting specific neuron functions from biochemical attacks in the systemic circulation. In this respect, capillary ECs, which provide a junctional complex comprised of AJs and TJs and mediate paracellular solute transfer between the blood and the brain [219–222], are another BBB component structure. Intercellular cleft-spanning proteins (occluding and claudin) and junctional adhesion molecules are found in TJs [219,222]. The zona occluding protein family, which includes ZO-1, ZO-2, and ZO-3, interacts with actin to bind occluding and claudin to the cytoskeleton [223]. Cadherin is an AJ protein that acts as structural support and bridges the intercellular cleft [219,222]. Connexins (Cx) proteins' role in the junctional complex has recently received more attention [224,225]. Even though sticky characteristics are essential for adjacent cells, Cx proteins, unlike TJ and AJ proteins, do not establish a tight barrier between the connecting cytoplasm and surrounding cells [226].

4.5. Inflammatory Cytokines and Bioactive Kynurenines

The kynurenine (KYN) pathway possesses the ability to produce various miniature receptor agonists and bioactive components with a wide array of activities together with neurotoxic, oxidative, neuroprotective, antioxidative, anti-inflammatory, and immune properties. Inflammation stimulates key enzymes involved in the KYN pathway. Indoleamine 2 and 3-oxygenase (IDO 1) in the brain and surrounding tissues are the initial rate-limiting enzymes of the tryptophan metabolism. IFN- γ , a pro-inflammatory cytokine, stimulates formamidase in human microglial cells and macrophages, leading to augmented KYN synthesis. Kynurenic acid (KYNA), an endogenous antagonist of N-methyl-D-aspartate and α 7-nicotinic acetylcholine receptors, is synthesized by kynurenine aminotransferases (KATs) and it is associated with neurological and cognitive features [227,228]. Pyridoxal

phosphate (PLP), a cofactor along with the active form of vitamin B6, and a co-substrate, α -ketoacid, are required for KATs [229]. PLP deficiency has been linked to neurological illnesses such as Alzheimer's disease, Parkinson's disease, and epilepsy [230]. Furthermore, it was reported that about 20% of the elderly are noticed to have lower dietary vitamin B6 absorption. Additionally, vitamin B6 supplementation ameliorates cognitive performance in the elderly. It was projected that folate, vitamin B6, and vitamin B12 are related to cognitive performance [227,228]. IFN- γ induced kynurenine-3-monooxygenase (KMO) activities in human microglial cells and macrophages, responsible for augmented quinolinic acid (QA) synthesis. The stimulation of macrophages and glial cells triggers the augmentation of QA [231]. Furthermore, microglia cells are liable for the substantial augmentation of the kynurenine pathway (KP) branch that is noticed upon the stimulation of the immune system [232].

4.6. Neuroinflammatory Factors Regarding Innate Immune Activation Reflecting Their Neuropathological Changes

Microglia, the resident immune cells of the central nervous system (CNS), play an important role in innate immune responses by producing cytokines and chemokines, such as type I and II IFNs and TNF, that promote the expression of hundreds of interferon-stimulated genes (ISGs), such as those that participate in inflammatory cell infiltration [233,234]. Microglia also up-regulate the expression of numerous receptors and produce various chemokines after CNS injuries, such as chemokine (C-X3-C motif) receptor 1 (CX3CR1) and chemokine (C-C motif) receptor 2 (CCR2) [235]. Similarly, reactive astrocytes also express many of these receptors and chemokines, suggesting that astrocytes and microglia communicate via chemokines. Astrocyte release of chemokines is important for attracting peripheral and CNS myeloid cells to the lesion site. In models of traumatic injury and parasitic infection, astrocytes are a source of chemokine (C-C motif) ligand 2 (CCL2) [236,237]. Astrocytes have also been shown to produce chemokine (C-X3-C motif) ligand 1 (CXC3L1) and CXCL1, detected by monocytes and microglia, in response to viral infection and spinal cord injury, respectively [238–240].

After entry into the brain or activation within the brain, innate immune cells demonstrate a spectrum of phenotypes, ranging from pro- and anti-inflammatory states, and can express a variety of cytokines and chemokines, including IL-1 β , IFN- γ , and TNF, that contribute to neuroinflammation. Reactive astrocytes have a demonstrated role in modulating immune responses by releasing cytokines that stimulate microglia and macrophages to adopt either pro- or anti-inflammatory responses [241]. Some immune cells played an essential role as good markers for neurodegenerative disorders (Table 2).

Table 2. Role of immune cells in the pathogenesis of neurodegenerative diseases [242].

Immune Cells	Alzheimer's Disease	Parkinson's Disease	Multiple Sclerosis
Monocyte	A higher proportion of monocytes in the peripheral blood	Exerted pro-inflammatory effects and participated in repair of injured brain	Contributed to MS-associated neuroinflammation
Macrophage	Mediated the clearance and degradation of A β	Produced pro-inflammatory and anti-inflammatory factors	Infiltrating macrophages and microglia promoted the pathogenesis of MS
Dendritic Cell (DC)	Vaccination of DCs sensitized to A β generated antibody responses	Tolerogenic bone marrow-derived DCs induced neuroprotective regulatory T cells	Circulating myeloid DCs and lymphocyte like DCs
T Cell	Might act in either protective or damaging properties	T-cell levels are down-regulated in peripheral blood	MS traditionally recognized as a predominantly T-cell-mediated autoimmune disease
B Cell	Played an essential role in cerebral A β pathology	Memory B cell repertoire of PD patients might represent a potential source for biomarkers and therapies	Involved in neuroinflammation of cortical cells, leading to neuronal death

4.7. Neuroinflammatory Markers Targeted by Herbal Therapeutics

As previously stated, AD and PD are complex illnesses with different pathology. Still, their biochemical and physiological cascades are linked directly or indirectly to the same basic neuro-inflammatory processes. In this context, growing evidence supporting the role of neuroinflammation in neurodegenerative diseases, coupled with increasing knowledge of the biochemical pathways that govern the neuro-inflammatory response, have assisted in the development of drugs that inhibit multiple molecular targets. This paradigm shift occurred after single molecular target-driven drug discovery, which had previously been the most effective avenue to novel medications, failed to advance against multifactorial disorders such as AD and PD. Anti-cholinesterase for the treatment of AD provides symptomatic relief with no disease-modifying benefits and provides a moderate potential to slow the progression of the disease [243,244]. Moreover, various plant-derived compounds with anti-inflammatory properties exert their effects through different mechanisms of action. These mechanisms involve modulation of the cytokine system controlling NF- κ B and p38 MAPK pathways; this is supported by a substantial body of evidence obtained from both in-vivo and in-vitro studies [245]. This is advantageous because it avoids the 'one drug, one mechanism of action' scenario and is expected to improve clinical results in disorders linked to neuroinflammation, where several biochemical events and bio-receptors are active at the same time [243]. There is growing evidence that natural plant products work through interacting with pro-inflammatory mediators such as NO and TNF, which involves cytokine system modulation [245,246].

In CNS inflammation, pro-inflammatory cytokines, IL-1 and TNF- α are produced by microglia that actively participate in BBB interruption [79]. As a result, various phytochemical compounds in the treatment of AD are expected to reduce microglial activation and reduce the production of pro-inflammatory and anti-inflammatory cytokines. In this regard, Oridonin, a bioactive component isolated from *Rabdosia rubescens*, inhibits NO production as well as the expressions of iNOS, IL-1, and IL-6, all of which contribute to neuroinflammation and dementia [78]. Peng and co-workers reported that triggering nuclear factor erythroid 2-related factor 2 (Nrf2) and modulation of NF- κ B pathways, causes a reduction of TNF- α and IL-12 production [80].

5. Perspective and Future Suggestions

There are uncountable factors involved in the pathogenesis of neuroinflammation, it is a difficult task to identify or diagnose a few markers responsible for NDs. The NDs might be occurring due to augmentation in chronic inflammatory diseases. Exploring the mechanism of neuroinflammation and neurodegeneration connecting to general inflammation would be a fascinating part of future research. There is a requirement for proper diagnosis of markers responsible for NDs, as there are various markers that individually account for types of NDs. The probable preclinical phases could supply the best window for therapeutic or defensive access to the general and fundamental role of inflammation in neurodegenerative diseases.

6. Conclusions

In summary, results from this review showed that neuroinflammation plays a vital role in several neurodegenerative diseases. The neuroinflammatory process occurs due to the overactivation of glial cells present in the CNS and the secretion of various neuroinflammatory markers such as TNF- α , IL-1 β , iNOS, COX-2, and ROS, among others. Overactivation of glial cells (astrocytes and microglia) in the CNS, causes the release of different inflammatory mediators and triggers various neurodegenerative diseases. As a result, neuroglial activation may provide an effective involvement to control the pathophysiology of neuroinflammation in neurodegenerative diseases. Different therapeutic approaches are very suitable in the treatment of various neuronal diseases; these include NSAIDs, monoclonal antibodies, nutraceuticals, gene knockout, and many others. However, there is

a need to explore more novel approaches and strategies for treating neuroinflammation and suppression of related markers and pathways.

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