NEUROSCIENCE RESEARCH NOTES

Neuroinflammation-induced neurodegeneration and associated microglia activation in Parkinson's disease: a novel neurotherapeutic avenue

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ABSTRACT: Parkinson's disease (PD) is classified as one type of neurodegenerative disorder. Movement disorder, which includes resting tremors and slowness of movement, is a common clinical symptom in PD patients. Neuroinflammation is one of the most important processes involved in the pathogenesis of PD. An inflammatory response in the brain can induce neuronal cell death. Microglia, a type of immune cell, plays a crucial role in neuroinflammation. In this review, we discussed the information on microglia-activated neuroinflammation, its relationship with PD, and therapeutic approaches for neuroinflammation in PD. Under normal conditions, microglia in their inactive state (M0) act as surveillance agents in the brain to investigate potential invasions. They regulate neuron production, remodel synapses, and secrete growth factors to protect the neurons. Under pathological conditions, the M0 transforms into active phenotypes, dividing into pro-inflammatory (M1) and anti-inflammatory (M2) microglia. The M1 and M2 microglia exhibit opposite functions, where M1 microglia promote pro-inflammatory responses, and M2 microglia promote anti-inflammatory responses. This dichotomy of functions is essential for maintaining a healthy level of inflammation in the brain. Presently, multiple therapeutic strategies are available for PD, encompassing anti-inflammatory drugs, neuroprotective compounds, antioxidants, nanoparticles targeting neuroinflammation, stem cell interventions, lifestyle adjustments, and microglia-focused treatments. These treatments improve patients' movement, allowing them to have lifestyles like others, consequently benefiting their mental and emotional well-being. Preventing microglia from polarising into the M1 phenotype and promoting their polarisation into the M2 phenotype could be a challenging and promising approach for treating PD.

Keywords: Neuroinflammation; Neurodegenerative disease; Microglia; Parkinson's disease

1.0 INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurological disease that mostly affects the elderly population. According to the 2020 report, there are more than 10,000,000 persons with Parkinson's disease globally, representing 0.124% of the population (Fang et al., 2020). The clinical signs include rigidity, postural instability, tremor, and slow movement. Dopaminergic neurons of the substantia nigra pars compacta (SNpc) have been shown to degenerate, which is linked to pathogenesis (Jiang et al., 2018). Because the disease has many causes, such as oxidative stress and inflammation, treating PD by suppressing the underlying cause still leaves room for incomplete development (Olanow, 2007; Yacoubian & Standaert, 2009; Buendia et al., 2016). The treatment of PD is still incomplete as it is only based on symptom management. The treatment of the underlying cause is crucial and can potentially result in a decelerated rate of disease progression. Hence, developing PD treatments based on their underlying causes is particularly challenging for researchers.

The aetiology of PD is mainly related to genetic and environmental factors (Li et al., 2019). However, the precise pathogenic pathways underlying PD are still not completely understood. Increased oxidative stress, mitochondrial failure, excitotoxicity (the overactivation of glutamate receptors), and neuroinflammation have recently been proposed as pathways causing neurodegeneration in PD (Olanow, 2007; Yacoubian & Standaert, 2009; Buendia et al., 2016; Sobhon et al., 2023a). One of the causes of PD is mitochondrial dysfunction, which results in increased reactive oxygen species (ROS) and reactive nitrogen species (RNS) production in dopaminergic neurons and ultimately causes neurodegeneration (Zhang et al., 2017). In addition, a large body of evidence from genetically and neurotoxin-induced animal models and human PD brains suggests neuroinflammation is a long-lasting aspect of the illness and contributes to neurodegeneration (Wang et al., 2020).

2.0 PARKINSON'S DISEASE

Parkinson's disease is a heterogeneous neurodegenerative condition influenced by genetics, environment, and individual variations, with an increasing global prevalence. While it is treatable through personalised approaches, there is currently no cure, but research into disease-modifying treatments is ongoing (Bloem et al., 2021). The pathological features of PD that are widely accepted are α-synuclein accumulations known as Lewy bodies and loss of dopaminergic neurons in the SNpc results in a significant decrease in the amount of dopamine released by dopaminergic neurons in the striatum (Kouli et al., 2018).

As a result, movement abnormalities occur due to a reduction in the function of dopaminergic neurons in the nigrostriatal pathway and an increase in the activity of cholinergic neurons, which become relatively more dominant (Zhang et al., 2017). The aetiology, however, is mainly influenced by genetic and environmental factors (Li et al., 2019). However, the explicit pathogenic mechanisms of PD have not yet been fully clarified. Researchers have hypothesised various pathogenic mechanisms over the years, including abnormal protein clearance leading to α-synuclein accumulation, mitochondrial dysfunction, excessive ROS and RNS production in dopaminergic neurons, dopamine transporter (DAT) inactivation, cell apoptosis, and inflammatory activity in the brain (Zhang et al., 2017; Li et al., 2019; Sobhon et al., 2023b). Due to the multitudinous aetiology of PD, there are not exactly efficient treatments for PD that can improve the initiated causes.

Early detection of PD can pose challenges due to the absence of a definitive test for the condition, and the initial symptoms can be subtle and often confused with other medical problems. The diagnosis of PD is mainly based on the clinical evaluation of motor symptoms such as bradykinesia, which occurs together with rigidity or tremor (Kobylecki, 2020). The early diagnosis of PD is useful, including consulting a neurologist or movement disorder specialist if abnormal movement occurs and performing a physical examination by a healthcare specialist.

There are many useful diagnostic tests in patients presenting with parkinsonism, such as magnetic resonance imaging (MRI) visualisation of substantia nigra neuromelanin (Ohtsuka et al., 2013; Wang et al., 2019), radiotracer imaging of α-synuclein and tau protein (Schonecker et al., 2019), and a blood test for neurofilament (Hansson et al., 2017). However, no biomarkers are available to provide an accurate diagnosis for any early stages of PD, with both high sensitivity and specificity (Tolosa et al., 2021). Many PD symptoms are manifested after dopaminergic neuron death. Thus, it is necessary to discover new and effective therapies that can decelerate or even reverse the progression of the disease, particularly the degeneration of dopaminergic neurons (Troncoso-Escudero et al., 2018).

The neurodegenerative mechanism of PD involves several processes, such as mitochondrial dysfunction, elevated levels of oxidative stress, excitotoxicity, and neuroinflammation (Olanow, 2007; Yacoubian & Standaert, 2009; Buendia et al., 2016). The onset and course of PD have all been linked to mitochondrial failure, oxidative stress, and neuroinflammation (Navarro & Boveris, 2009; Di Filippo et al., 2010; Brandes & Gray, 2020). In earlier studies, researchers found evidence of mitochondrial dysfunction in dopamine neurons located in the substantia nigra during the early stages of PD (Hattingen et al., 2009; Brandes & Gray, 2020).

Inflammation is also considered a significant factor contributing to the development of PD. The brain and cerebrospinal fluid (CSF) of PD patients were discovered to have higher levels of pro-inflammatory cytokines such as tumour necrosis factor (TNF-α) and interleukin-6 (IL-6) (Hirsch et al., 2012; Dzamko et al., 2015; Brandes & Gray, 2020). Indeed, it has been proposed that the pathophysiology of PD may be caused by a gut infection that causes inflammation, which then travels throughout the body (Bjarnason et al., 2005; Brandes & Gray, 2020)**.**

3.0 NEUROINFLAMMATION AND PARKINSON'S DISEASE
3.1 Microglia activation
Microglia, comprising about 10 to 15% of the central nervous system (CNS), are specialised immune cells crucial in CNS repair and regeneration (Fatoba et al., 2020). Microglia function as innate immune defenders of the CNS parenchyma, playing a vital role in monitoring the microenvironment of the CNS (Orihuela et al., 2015) and serving as the primary mediators of neuroinflammation (Fatoba et al., 2020).

Under normal physiological conditions, microglia exhibit a resting state known as M0, characterised by small bodies and long, thin processes. Although resting microglia cannot present phagocytic functions, they can move, display pinocytosis, and secrete growth factors supporting and protecting the neurons to maintain CNS homeostasis (Zhang et al., 2021a). After activation by stimuli, resting microglia transform into two types of activated microglia depending on exposure to different microenvironments, including M1 (the classical phenotype) and M2 (the alternative phenotype) for maintaining CNS homeostasis (Guo et al., 2022).

For M1/M2 phenotype markers, the activation of resting microglia is induced via factors released from type 1 T helper (Th1) and type 2 T helper (Th2) cells. Interferon-γ (IFN-γ) produced by Th1 cells stimulates M1 microglia polarisation and proliferation, whereas anti-inflammatory IL-4 released by Th2 cells stimulates M2 microglia polarisation (Jurga et al., 2020).

3.1.1 M1 microglia
Pro-inflammatory cytokines such as TNF-α and IFN-γ and cellular or bacterial debris can cause microglia to transform from a resting state to an M1 pro-inflammatory phenotype. The M1 phenotype of microglia subsequently secrete pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-12, and IL-23, present antigen, and express high amounts of inducible nitric oxide synthase (iNOS) for NO generation from the enhanced switching of oxidative metabolism to glycolytic metabolism to sustain energy for microglia activities (Orihuela et al., 2015). Although M1 microglia can facilitate phagocytosis, eliminate pathogens, and promote tissue repair, the overproduction of pro-inflammatory cytokines, iNOS, and ROS can lead to chronic inflammation and worsen neurodegenerative disorders.

Several stimuli can induce the M1 phenotype of microglia, including double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), and unmethylated CpG islands in stretches of DNA derived from viral infection. In addition, microbial products, such as lipoteichoic acid (LTA) and lipopolysaccharide (LPS), can also activate M1 microglia by binding to specific toll-like receptors (TLR), including TLR2, TLR3, TLR4, TLR7, and TLR9. The activation of TLR2/4, myeloid differentiation primary response 88 (MYD88), and/or TIR-domain-containing adapter-inducing interferon (TRIF) leads to the activation of several transcription factors, including interferon regulatory factors (IRFs), NF-κB, activator protein 1 (AP-1), and activator of transcription 5 (STAT5).

This activation results in the production of iNOS, as well as the upregulation of various cell surface markers, such as major histocompatibility complex class II (MHCII), cluster of differentiation (CD) 86, and CD16/32, as well as pro-inflammatory cytokines and chemokines, such as TNF-α, IL-6, IL-1β, IL-12, chemokine (C-C motif) ligand 2 (CCL2), and C-X-C motif chemokine ligand 10 (CXCL10) (Moehle & West, 2015).

3.1.2 M2 microglia
M2 is a distinct type of microglia that releases anti-inflammatory substances and generates protective proteins in the extracellular matrix. This leads to

activities such as wound healing, removing cellular debris, suppressing inflammation, and restoring homeostasis (Jurga et al., 2020).

Activated M2 microglia can be categorised into three different subclasses: M2a, M2b, and M2c. These subclasses possess distinct characteristics and have minimal overlapping features. In M2a, the IL-4 specifically binds to IL-4 receptor (IL4R), which activates JAK1/3. This, in turn, causes the translocation of STAT6, a protein-coding gene, to the nucleus, resulting in the upregulation of various genes such as arginase-1, suppressor of cytokine signalling 1 (SOCS1), CD206, and scavenger receptors (SRs). The activation of the M2a state also results in the release of IL-10 and polyamines.

The M2b phenotype has similarities with the M1 phenotype, including the presence of CD86 on the cell surface, the release of certain cytokines such as IL-6, IL-1β, and TNF-α, which is triggered by IgG binding to the Fcγ receptor (FcγR). The activation of the M2b phenotype occurs through the RAS, PI3K, and Syk signalling pathways. These pathways cause mitogen-activated protein kinase (MAPK) translocation to the nucleus and subsequent expression of CD86, TNF-α, IL-6, IL-1β, as well as IL-10.

Another phenotype, the M2c, is activated via IL-10 binding to a heterodimer of IL-10 receptors 1 and 2 (IL10R1 and IL10R2), which leads to Janus kinase 1 (JAK1) and tyrosine kinase (tyk) activation, and then induces translocation of STAT3 into the nucleus and upregulates surface lipoprotein assembly modulator (SLAM) and CD206, as well as increased release of IL-10, transforming growth factor-β (TGF- β), and extracellular matrix proteins (Moehle & West, 2015).

To identify the M2 microglia, CD206, a surface protein receptor specific to pathogenic glycoproteins and polysaccharide chains responsible for endocytosis, can be determined (Jurga et al., 2020). Additionally, certain anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1Ra), IL-4Ra, IL-4, TGF, and IL-10 are markers for identifying M2 microglia. M2 microglia also secrete chemokines, such as CCL2, CCL17, CCL22, and CCL24, to suppress ongoing inflammation. The enzyme Arginase 1 (Arg1) converts the amino acid arginine into ornithine and urea. These molecules are subsequently broken down into proline and polyamines, essential for tissue remodelling and wound healing. As iNOS and Arg1 both utilise arginine as a substrate, it is prudent to evaluate the ratio of these enzymes in activated microglia. This comparison can provide useful insights into the balance between pro-inflammatory and anti-inflammatory responses in microglia.

The ability to distinguish between M1 and M2 is made possible by the downregulation of NO production and iNOS expression that results from Arg1 overexpression (Jurga et al., 2020). The M2 phenotype of microglia has neuroprotective effects on the brain in contrast to the M1 phenotype's damaging effects. It is suggested that a potential strategy to treat neurodegenerative diseases involves hindering the polarisation of microglia into the M1 phenotype and promoting their polarisation into the M2 phenotype. This approach can help maintain the balance between anti-inflammatory and pro-inflammatory responses, which are crucial in neurodegenerative diseases (Jurga et al., 2020).

3.2 Microglia induces neuroinflammation

The inflammatory response in the CNS, known as neuroinflammation, results in additional brain tissue damage and subpar functional recovery (Zhang et al., 2021a). Astrocytes, neurons, and microglia, as well as infiltrating T-cells and neutrophils, mediate neuroinflammation. Additionally, inflammatory mediators produced by these cells play a role in this process (Kempuraj et al., 2016).

In normal conditions, the blood-brain barrier (BBB) plays a critical role in maintaining the healthy functioning and development of the brain by regulating the transport and permeability of molecules between the extracellular fluid and plasma. Consequently, different immune cell types cannot translocate into the brain under abnormal conditions, such as aggregation of misfolded proteins and accumulation of abnormally modified cellular components (Zaragoza, 2020). The initial stage involves interaction between damaged tissue and pattern recognition receptors (PRRs), protein receptors like TLR. PRRs recognise molecules typically present in pathogens called pathogen-associated molecular patterns (PAMPs) or molecules discharged by damaged cells known as damage-associated molecular patterns (DAMPs). Examples of DAMPs include dsDNA, RNA, and proteins enriched in the brain. Microglia activation occurs due to this process (Lv et al., 2023).

Microglia regulate protective and harmful responses to the damaged brain and are important regulators of the immune response in neurodegenerative disease (Simpson & Oliver, 2020). These activated microglia bring on the phagocytosis, antigen presentation, and synthesis of pro-inflammatory cytokines. Active microglia express co-stimulatory molecules like CD40,

CD45, CD80, and CD86, and proteins like lymphocyte function-associated antigen 1, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1). These molecules make the BBB more permeable, enabling active T lymphocytes to cross it and enter the brain parenchyma. Upon recognition of their specific antigen, the infiltrated T lymphocytes activate the NF-κB signalling cascade. This activation prompts the T lymphocytes to produce pro-inflammatory cytokines. These subsequently attract immune cells, including neutrophils and monocytes, to the injury site, where they produce RONS, which cause damage to macromolecules, including proteins and DNA.

The accumulation and activation of inflammatory cells or increased peripheral immune and inflammatory activities subsequently induce progressive cell death, resulting in neurodegenerative diseases (Thelin et al., 2017; Amarante-Mendes et al., 2018; Nzogang & Donkeng, 2020; Saha et al., 2020). The pathogenesis of several inflammatory diseases involves the activation of the NF-κB signalling pathway. Consequently, one of the therapeutic strategies for treating such diseases is to inhibit the activity of NF-κB (Liu et al., 2017).

3.3 The relationship between neuroinflammation and Parkinson's disease

CNS inflammation is a major contributor to neurodegenerative disorders (Leonoudakis et al., 2017). Neurodegeneration is the progressive loss of functional neurons and structure (Chen et al., 2016; Timmerman et al., 2018). The initial study of PD in 1988 discovered that neuroinflammation was involved in neurodegeneration because activated microglia were located in the substantia nigra (SN) of PD brains (Tai et al., 2013). More research is now demonstrating that neuroinflammation is a long-lasting aspect of the disease and contributes to neurodegeneration in animal models of PD as well as human PD brains and genetically and neurotoxin-induced animal PD models (Wang et al., 2020).

Inflammation is one of the pathological hallmarks of PD (Moehle & West, 2015). Microglia have an important role in neuroinflammation, are involved in the pathogenesis of PD, and are negatively correlated with dopaminergic neuron survival in patients (Saitgareeva et al., 2020). Reactive microglia, which is microglial cells that have undergone a response to a pathological condition or a disturbance in the CNS, and Lewy bodies are both present in the substantia nigra of patients with PD (McGeer et al., 1988).

Moreover, post-mortem studies indicated that in PD patients, activated microglia are close to neurons that exhibit pathological accumulation of α-synuclein (Croisier et al., 2005). An *in vitro* study provided additional evidence to support the idea that there is a link between α-synuclein-induced microglial migration and accumulation in the substantia nigra. This discovery indicated that α-synuclein acted as a chemoattractant, attracting microglia toward it. The membrane type 1-matrix metalloproteinase (MMP) may have assisted this chemoattractant ability. Additionally, the increase in soluble CD44, a cell adhesion molecule, was found to be involved in this process, releasing microglia from the surrounding matrix and allowing them to migrate (Kim et al., 2009).

The other pathway involved in neuroinflammation is the nuclear factor-κB (NF-κB) signalling pathway. The NF-κB signalling pathway is a widely recognised inflammatory transcription factor that contributes to the progression of neurodegenerative conditions (Sun et al., 2022). The NF-κB signalling pathway is upregulated in M1 microglia by several stimuli. The NF-κB signalling pathway can be activated by the binding of 1-methyl-4-phenylpyridinium (MPP$^+$), which is a neurotoxin, to specific receptors located on the surface of microglia cells (Zhou et al., 2016). After stimulation, the I kappa B (IκB) kinase (IKK) complex will be stimulated to phosphorylate the IκB protein, which is NF-κB holder in the cytosol. The phosphorylated IκB will detach from NF-κB and be degraded. After becoming free, NF-κB will activate and move into the nucleus. In the nucleus, it will enhance the expression of various pro-inflammatory mediators, including TNF-α, IL-1β, and IL-6, as well as adhesion molecules like ICAM1 and enzymes involved in inflammation such as cyclooxygenase-2 (COX-2) and iNOS (Liu et al., 2017).

IL-1β can induce the transformation of M0 into M1. At the same time, ICAM1 can increase the permeability of the BBB, resulting in the entry of helper T cells and other immune cells from the peripheral system into the brain. Th1 and Th17 cells also produce TNF-α, which helps promote the transformation of M0 to M1, similar to the function of IL-1β. Th2 can produce anti-inflammatory cytokines like IL-4 and IL-10. These anti-inflammatory cytokines will accelerate the development of M0 into M2 (Jurga et al., 2020). The pro-inflammatory mediators produced by the NF-κB signalling pathway in microglia are shown in **Figure 1**.
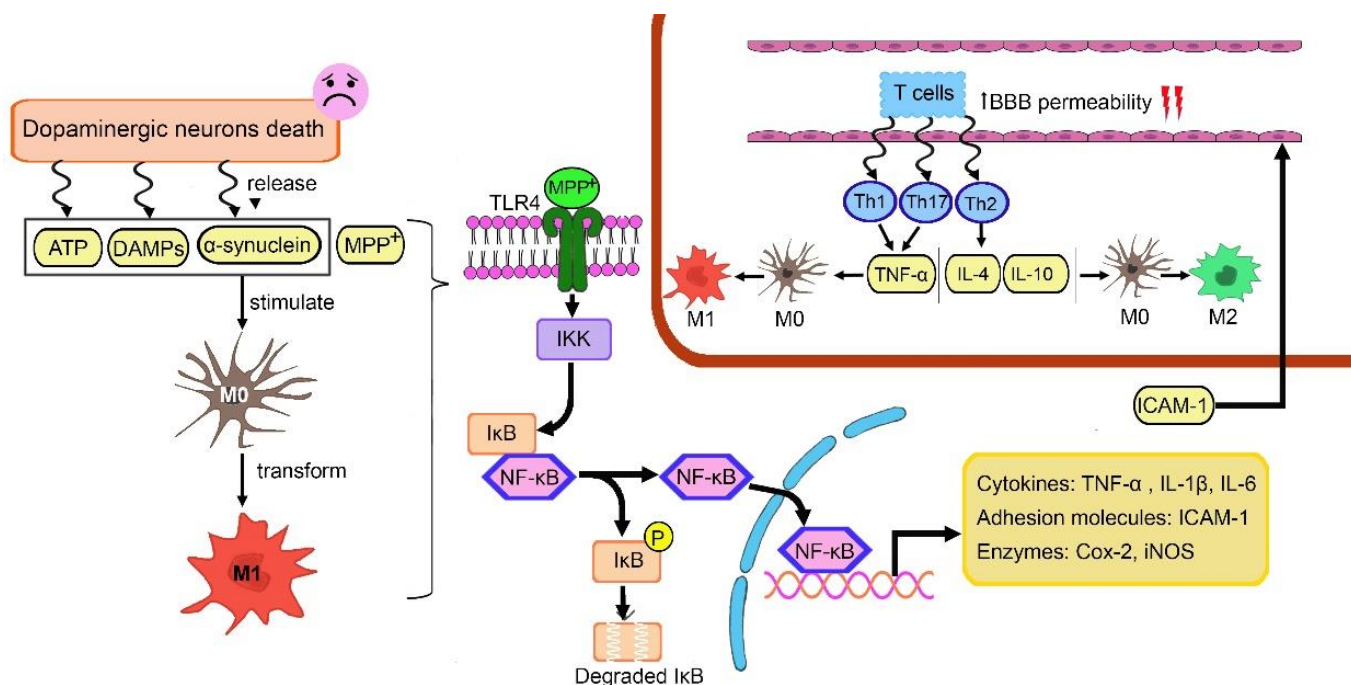
Figure 1. Pro-inflammatory mediators produced by NF-κB signalling pathway in M1 microglia and their target actions. M0, M1, M2: Microglia cell types; ATP: Adenosine triphosphate; DAMPs: damage-associated molecular patterns; MPP$^+$: 1-methyl-4-phenylpyridinium; TLR4: toll-like receptor 4; IKK: I kappa B (IκB) kinase; NF-κB: nuclear factor-κB; P: phosphate; Th1, Th2, Th17: T-helper cell types; TNF-α: Tumour necrosis factor; IL-1β, IL-4, IL-6, IL-10: Interleukin types; ICAM-1: intercellular adhesion molecule 1; Cox-2: cyclooxygenase-2; iNOS: inducible nitric oxide synthase.

M1 and M2 release and express different cytokines and proteins, as shown in **Figure 2**. TNF-α, IL-1β, IL-18, and CD86, as well as an inducible nitric oxide synthase (iNOS), are all produced by M1 microglia. Cytokines released from M1 microglia can bind to specific receptors on the surface of dopaminergic neurons and activate the apoptosis pathway. Meanwhile, iNOS present in M1 microglia can convert arginine to nitric oxide (NO), which can travel to dopaminergic neurons and damage the mitochondria. This damage leads to the overproduction of superoxide anions (O_2^-) or ROS, which can cause further harm to the neurons. The death of dopaminergic neurons is then brought on by the production of apoptosis and excessive ROS (Shen et al., 2017a).

However, M2 microglia, identified by the M2 marker CD206, can also release various anti-inflammatory mediators, including IL-6, IL-10, IL-13, and Arg1. IL-13 can suppress the Th1 function while inducing the Th2 function (**Figure 2**) (Nakagawa & Chiba, 2014). IL-10 can suppress Th1 and inhibit neuronal cell apoptosis and NO production (Couper et al., 2008). IL-6 can inhibit NO production and support synapse survival (Hung et al., 2010; Kummer et al., 2021). Furthermore, Arg1 can

convert arginine to ornithine, which can be converted to proline and polyamide, both capable of collagen synthesis. Arg1 can induce the synthesis of glutathione, which is a crucial antioxidant (Ricciardolo et al., 2005). The actions of anti-inflammatory mediators ultimately result in the protection of dopaminergic neurons, safeguarding their function and viability. In summary, an imbalance between M1 and M2 microglia, with a predominance of M1, can lead to the accelerated loss of dopaminergic neurons, heightening the likelihood of developing PD in the future.

As mentioned earlier, α-synuclein aggregation is one of the neuropathological hallmarks of PD and correlates with microglia activation (Song et al., 2021). The pathological forms of α-synuclein deposited in cells are characterised by aggregation and reduced solubility compared to the normal protein (Cookson, 2009; Bandopadhyay, 2016). The level of detergent-insoluble α-Synuclein extracted from the brains of patients with PD was higher than that found in individuals without the condition (Kahle et al., 2001). These pathological forms of α-synuclein may disrupt the communication between neurons at synapses, ultimately resulting in the death of neuronal cells (Cookson, 2009).

Molecules such as extracellular matrix (ECM), lysophosphatidylcholine (LPC), colony-stimulating factor 1 (CSF-1), CCL2, MMP3, and ATP can be expressed by dead dopaminergic neurons and have the potential to activate resting microglia and transform them into phagocytic cells. Pro-inflammatory mediators like MMP disrupt the BBB, which causes peripheral immune cells (activated T-cells) to infiltrate the brain and produce more inflammatory chemicals. This intensifies neuroinflammation and neurodegeneration.
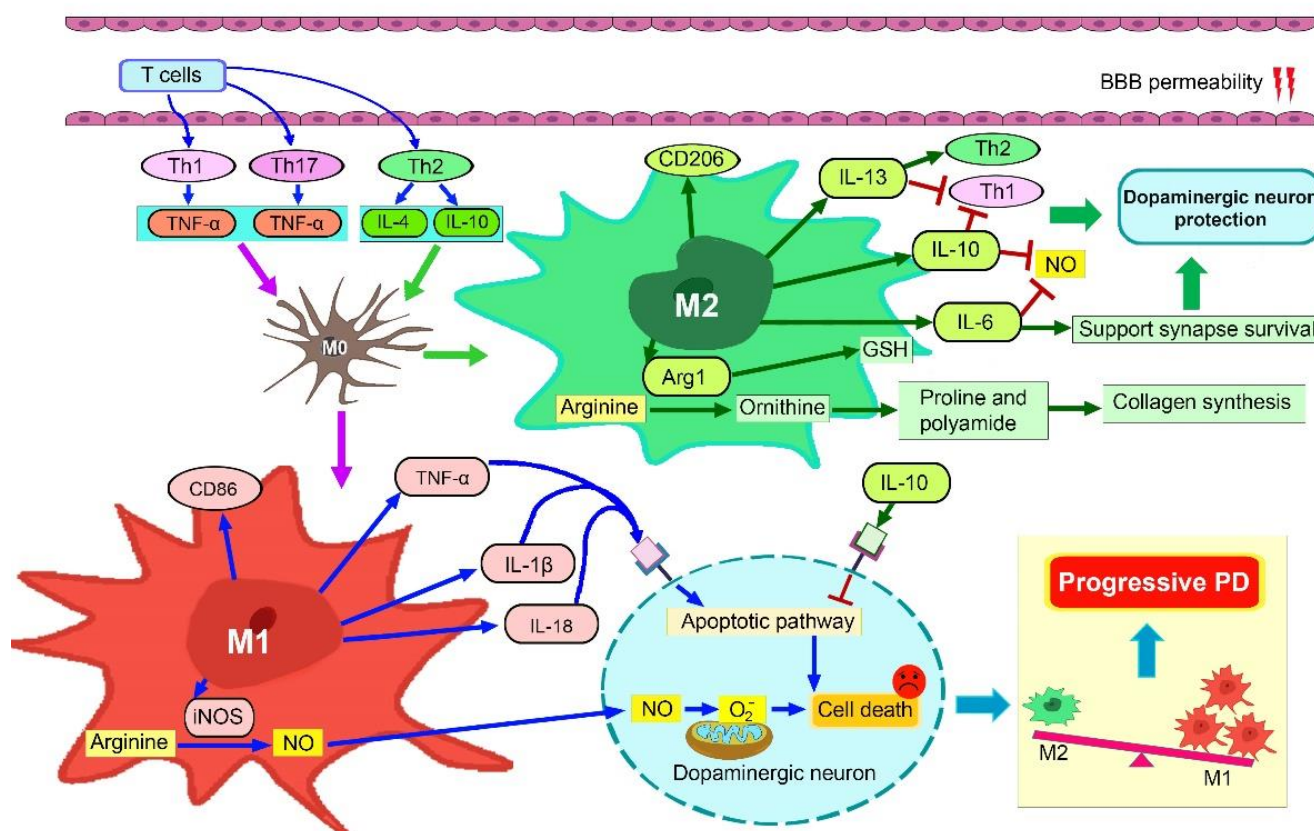

Figure 2. The roles of inflammatory mediators produced from M1 and M2 microglia in damaging and protecting dopaminergic neurons. M0, M1, M2: Microglia cell types; Th1, Th2, Th17: T-helper cell types; TNF-α: Tumour necrosis factor; IL-1β, IL-4, IL-6, IL-10, IL-13, IL-18: Interleukin types; CD86, CD206: cluster of differentiation; iNOS: inducible nitric oxide synthase; NO: nitric oxide; PD: Parkinson's disease; Arg1: Arginase 1; GSH: glutathione; BBB: Blood brain barrier.

Moreover, α-synuclein released from neurons can directly interact with TLRs expressed on microglial cells, resulting in a microglial-mediated inflammatory response and neuroinflammation (Fatoba et al., 2020). When neurons are injured, the released α-synuclein leads to microglia M1-like phenotype polarisation and activates microglia via endogenous TLR2 and TLR4. For the intracellular signalling pathway through TLR2, the NLR family pyrin domain-containing 3 (NLRP3) pathway is activated. This causes the inflammasome to become fully active, and the release of IL-1β causes inflammation. On the other hand, α-synuclein-binding TLR4 leads to transcriptional upregulation of p62 via the NF-κB signalling pathway (Lv et al., 2023). Moreover, α-synuclein aggregation will increase the generation of

oxidative stress induced by neuroinflammation, and an excessive amount of ROS will promote more neuroinflammation and α-synuclein aggregation, so establishing a positive feed-forward loop (Frenneaux & Williams, 2007; Zheng & Zhang, 2021).

In ageing or degenerating brains, microglia tend to exhibit M1-like characteristics which include reduced branching and beading of their processes, upregulation of M1-markers (MHCII, CD86, and CD16/32, and pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-12), and a concurrent decrease in the levels of anti-inflammatory mediators such as IL-10, brain-derived neurotrophic factor (BDNF), and IκB inhibitors (Simpson & Oliver, 2020). Several studies have shown that α-

synuclein accumulation, which is released from dead dopaminergic neurons into the extracellular space, can directly induce resting microglia to transform into the M1 phenotype (Marques & Outeiro, 2012; Shen et al., 2017b; Troncoso-Escudero et al., 2018; Lv et al., 2023).

This microglia activation results in an increase in ROS and pro-inflammatory cytokines such as TNF-α and NO production. Furthermore, LPS stimulated microglia, which lack α-synuclein, induced TNF-α and IL-6 secretion, and reduced phagocytic capacity (Saitgareeva et al., 2020). The initial discovery of a gene linked to PD, known as synuclein alpha (SNCA) (Polymeropoulos et al., 1997). The mutant α-synuclein gene led to overexpressing the α-synuclein expression from SH-SY5Y. This protein can trigger microglia activation to increase producing NO, IL-1β, TNF-α, and ROS (Lee et al., 2010).

Another evident, BV2, microglia cell line, transfected cDNA coding over-expression of mutant a-synuclein increased pro-inflammatory secretion (TNF-α) and Cox-2 levels in BV2 cells (Rojanathammanee et al., 2011). The other gene involved in PD, leucine-rich repeat kinase 2 (LRRK2) missense mutations, causes late-onset PD. Moehle and colleagues (2012) showed that suppressing LRRK2 kinase function reduces pro-inflammatory signalling in microglia. Another gene involved in PD is PTEN-induced kinase 1 (PINK1). PINK1, working with Parkin, regulates the clearance of damaged mitochondria in cells within the CNS. When PINK1 mutates or is absent in neurons, there is an increase in ROS production and damage to mitochondrial DNA, ultimately leading to dopaminergic neuron cell death. Furthermore, the absence of PINK1 in astrocytes and microglia could potentially increase ROS production and activate inflammatory responses in PD (Leites & Morais, 2021).

Earlier research found robust microglia activation with parallel inflammatory factors in brain regions under attack. Increased levels of IL-1β, TNF-α, ROS, and NO have been found in PD patients' substantia nigra and corpus striatum, as well as cerebrospinal fluid and serum (Jurga et al., 2020). The NO produced in microglia may be toxic to dopaminergic neurons. Aside from α-synuclein accumulation and dopaminergic neuron degeneration in the SNpc, inflammation is important in PD.

SNpc has high numbers of microglia involved in the inflammatory response. Microglia have a role in the clearance of neuronal cell death debris. However, the debris from neuronal cell death can activate microglia, producing and releasing inflammatory factors such as pro-inflammatory cytokines and chemokines, as well as RONS. Hence, the neuroinflammatory response may contribute to the progression of PD pathology. In addition to microglia activation, a variety of neuroinflammatory factors have been identified in the brains of PD patients, including elevated levels of IFN-γ, TNF-α, IL-1β, and IL-6 in the striatum and substantia nigra of PD patients in comparison to healthy controls (Bachiller et al., 2018).

The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is a neurotoxin that can cause parkinsonism in model systems by destroying dopaminergic neurons in the substantia nigra. The enzyme MAO-B converts MPTP to MPP$^+$ in the glial cells, which then enters the neuron through DAT and disrupts the electron transport chain in the mitochondria (Hare et al., 2013). This leads to oxidative stress, causing damage to the neurons. Robust inflammation is a frequent observation in MPTP models of dopaminergic cell death.

The characteristics of the M1 phenotype of microglia are found in the MPTP intoxication model, including releasing various pro-inflammatory mediators and activity of NF-κB pathways. The two microglia phenotypes can transition into each other. The phenotype switching might be the strategy for activating the protective function of microglia (Saitgareeva et al., 2020). Some neuroprotection is achieved by blocking MPTP-induced M1 inflammation. Anti-inflammatory treatment and pro-inflammatory gene ablation, for example, iNOS, can protect dopaminergic neurodegeneration.

Due to their capacity to cause cell death and microglial activation, MPTP, 6-hydroxydopamine (6-OHDA), and LPS are hazardous chemicals frequently employed to imitate PD mouse models. Strong neuronal loss and activation of microglia in the SNpc are demonstrated using the MPTP model. The mouse model of PD induced by MPTP provided evidence that several TLRs (TLR3, TLR4, TLR7, and TLR9), along with the MyD88 gene (key adaptor in the TLR signalling pathway), were shown to be involved in mediating cell death in the mouse model of Parkinson's disease induced by MPTP (Ros-Bernal et al., 2011; Noelker et al., 2013).

According to further studies conducted using a mouse model, it was found that the inflammatory response induced by LPS led to a significant and strong reaction from the macrophages and microglia in the substantia

nigra, with the macrophages demonstrating a tendency to cluster around blood vessels. Compared to the striatum, the substantia nigra displayed a greater sensitivity to the inflammatory stimulus, suggesting that it is more susceptible to inflammatory reactions (Herrera et al., 2000). Moreover, in an animal model of intranigral LPS injection, the microglia inhibitor minocycline was administered, and the results demonstrated that dopaminergic neurons were protected and levels of TNF-α, IL-1β, and protein peroxynitrite were decreased in comparison to mice that were not given the medication (Bachiller et al., 2018).

The main pathways associated with the inflammatory process in PD include the NF-κβ, mitogen-activated protein kinase (MAPK), and C-Jun N-terminal Kinase (JNK) pathways. Inhibiting NF-κB in microglia in the mouse model exposed to MPTP protects neurons in the nigra-striatum pathway. It enhances motor function by reducing activation and production of TNF-α, IL-1β, and iNOS in the SNpc (Bachiller et al., 2018). An endogenous peptide called carnosine, or β-alanyl-L-histidine, is present in the liver, skeletal muscle, and brain.

Carnosine pre-treatment has been shown to have the potential to mitigate oxidative stress, inflammatory damage, and dopaminergic neuron death in male C57BL/6 mice induced with MPTP. This is achieved through several mechanisms. Firstly, it increases the levels of glutathione (GSH) and carnosine. Secondly, it boosts the activity of glutathione peroxidase (GPX) and superoxide dismutase (SOD). Thirdly, it reduces the levels of IL-6 and TNF-α. Fourthly, it inhibits the generation of NO and iNOS. Finally, it regulates the mRNA expression of GPX and iNOS in the striatum, which has an impact on the levels of neurotransmitters such as dopamine (DA), catabolites homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DOPAC) (Tsai et al., 2010). MPP$^+$ stimulates microglial cell line, BV2, and cell inflammatory activity in a dose- and time-dependent manner via TLR4/NF-κB activation and pro-inflammatory secretion. A novel approach for reducing microglial inflammation in cellular and molecular events in the pathogenesis of PD may involve inhibiting the TLR4 signalling pathway (Zhou et al., 2016).

Vitamin D, which targets dopaminergic neurons, is crucial for brain function, and its deficiency affects nearly all brain function. Vitamin D levels are low in PD patients, and increasing vitamin D levels can potentially improve mood, cognition, and behaviour in PD patients and prevent the worsening of PD symptoms (Behl et al., 2022). Vitamin D was found to increase the expression of anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β while significantly decreasing the loss of dopaminergic neurons, microglial cell activation, and expression of pro-inflammatory cytokines in the MPTP-induced mouse model (Calvello et al., 2016).

Vitamin D may influence PD through its effects on immune responses, genetic factors, and neuroprotection. It has been linked to changes in the expression of various genes, including HO-1, the vitamin D receptor (VDR), and neurotrophic factors (NTFs). It also affects non-genomic factors such as nerve growth factor (NGF), MMPs, ROS, and nitric oxide synthase (NOS) in the PD (Luong & Nguyen, 2012). Vitamin D binding VDR acts to enhance Nrf2 translocation into the nucleus, leading to an increase in catalase, SOD, and HO-1 expression, resulting in countering ROS toxicity and also inhibiting NF-κB expression and translocation into the nucleus, leading to a reduction of iNOS (Cui & Eyles, 2022) in both *in vitro* and *in vivo* models (Kim et al., 2020; Hu et al., 2021).

Additionally, vitamin D can upregulate BDNF expression, which is NGF, in the male rat hippocampus (Abdollahzadeh et al., 2022), as well as downregulate MMP-9 in the TNF-α-induced human keratinocyte and consequently attenuate skin inflammation (Bahar-Shany et al., 2009). Moreover, a naturally occurring vitamin D called farrerol possesses anti-inflammatory by blocking the TLR4 signalling pathway. In MPP$^+$-exposed BV2, farrerol can reduce the inflammatory response in these cells. Furthermore, farrerol has been found to inhibit the activation of the TLR4/NF-κB signalling pathway as well as the overexpression of pro-inflammatory molecules such as IL-6, IL-1β, TNF-α, iNOS, and COX-2 (Cui et al., 2019). The activation of microglia involved in the inflammatory response in PD plays a major part in the pathology. However, the exact mechanism by which microglial cells are activated and how this affects neuronal survival remains unclear (Bachiller et al., 2018).

4.0 THERAPEUTIC APPROACH FOR NEUROINFLAMMATION IN PARKINSON'S DISEASE

Neuroinflammation is recognised as a contributing factor to the progression of PD. Presently, efforts are being made to develop treatments explicitly targeting neuroinflammation to combat PD. Several therapeutic approaches are currently employed for the treatment and prevention of neuroinflammation and microglia activation.

4.1 Anti-inflammatory medications

Anti-inflammatory medications can be used to suppress the production of pro-inflammatory cytokines and chemokines. Non-steroidal anti-inflammatory medicines (NSAIDs), glucocorticoids, and immunomodulatory compounds are examples of these medications.

4.1.1 Basic science evidence

There have been many studies done on the effects of NSAIDs in neuroprotection from neuroinflammation in Parkinson's disease models, as indicated in **Tables 1 and 2**. In addition to NSAIDs, immunomodulatory drugs can be used to treat neuroinflammation. Monoclonal antibodies, for example, can attach to specific immune cells or inflammatory chemicals involved in neuroinflammation, inhibiting their activity (Castelli et al., 2019).

4.1.2 Clinical evidence of anti-inflammatory agents on PD

The meta-analysis on NSAIDs and risks of PD concluded that some NSAIDs, for example, aspirin or acetaminophen (Gagne & Power, 2010), did not have a significant effect on the risk of developing PD (Ren et al., 2018). In contrast, non-aspirin NSAIDs such as ibuprofen were associated with a 27% reduction in the risk of developing PD. It means ibuprofen may protect against PD (Rees et al., 2011; Gagne & Power, 2010; Gao et al., 2011; Samii et al., 2009). A few examples of studies that have explored the effect of NSAIDs in people with and without PD conditions are represented in **Table 3**.

Although NSAIDs could be beneficial in PD, there are side effects after the use of NSAIDs. NSAIDs have known risks, such as gastrointestinal and cardiovascular complications, so their use should be carefully considered based on the patient's clinical needs, particularly in the elderly (Poly et al., 2019). Further research is needed to understand the exact mechanisms underlying this relationship and to explore the optimal dose and duration of use.

4.2 Neuroprotective agents

Neuroprotective drugs can help prevent brain cell damage and enhance brain cell healing. Growth factors such as BDNF and neurotrophic factors such as nerve growth factor (NGF) are examples of these medicines (Sims et al., 2022). In an in *vitro* investigation, NGF considerably reduced the robust pro-inflammatory response to LPS-induced monocytes by reducing NF-κB, IL-1β, and IL-6 mRNA levels (Prencipe et al., 2014). Intracisternal BDNF infusions significantly reduced inflammatory cytokines, including IL-1β, TNF-α, and NF-κB, in female rats infected with *Streptococcus pneumoniae meningitis*. However, this response was blocked when a TrkB receptor inhibitor, which plays a crucial role in activating the PI3K/Akt pathway promoting neuronal survival by regulating proteins involved in cell survival, was co-administered (Romeika et al., 2017; Xu et al., 2017).

Additionally, monoamine oxidase B (MAO-B) inhibitors, such as selegiline and rasagiline, are neuroprotective drugs that can elevate and extend synaptic dopamine levels. The rasagiline studied the effect in DJ-1 deficit N9 murine microglial cells by Trudler and colleagues (2014). The results showed that rasagiline-treated DJ-1 deficit N9 microglia greatly decreased ROS, NO, IL-1β and IL-6 production and increased the survival of rotenone-induced SN4741 neuronal cells. Furthermore, safinamide, another MAO B inhibitor, studied the effect of the 6-OHDA-induced animal model by Neuroprotection by Sadeghian and colleagues (2015). The results demonstrated that using safinamide can diminish microglia activation and the loss of dopamine-producing neurons.

4.3 Antioxidants

Neuroinflammation is exacerbated by oxidative stress. Antioxidants like vitamins E and C can help minimise oxidative stress and protect brain cells from harm (Jelinek et al., 2021). Vitamin C (ascorbate, ascorbic acid) is a potent antioxidant. PD mouse model (MPTP-induced male mice) was treated with vitamin C (15 mg/Kg) daily for 10 days through intragastric gavage. The results demonstrated that vitamin C effectively reduced the loss of TH-positive dopaminergic neuronal cells in the substantia nigra induced by MPTP. Notably, vitamin C also suppressed the production of inflammatory cytokines, including IL-6, TLR4, TNF-α, iNOS, and CD40 at both protein and mRNA levels, while simultaneously increasing the expression of anti-inflammatory proteins such as IL-10, CD163, TGFβ-, and IL-4.

Furthermore, vitamin C inhibited NLRP3 activation, a process implicated in the pathophysiology of various inflammatory diseases, including neuroinflammatory disorders (De Nuccio et al., 2021). Vitamin E (α-tocopherol) is another powerful antioxidant that can block the propagation of ROS chain reactions, primarily in membrane lipids (Jelinek et al., 2021). The homozygous PTEN-induced kinase 1 knockout (PINK1−/−) mouse model of PD was treated with Vitamin E soluble in water. PINK1-/- animals have

unusual synaptic plasticity changes at corticostriatal synapses, including the loss of both long-term potentiation and long-term depression and were restored entirely to corticostriatal synaptic plasticity, indicating a particular protective function. Vitamin E may certainly compensate for PINK1 haploinsufficiency and mitochondrial dysfunction, reversing some key steps in the pathogenic process (Schirinzi et al., 2019).

Table 1. Anti-inflammatory drugs have effects on Parkinson's disease cell models.

Molecule	Models	Mechanism	Response	References
Oxicam	MPP$^+$-induced SH-SY5Y	Anti-apoptosis	▪ Suppression of the ER stress response and mitochondrial dysfunction caused by Akt activation	(Omura et al., 2018)
Aspirin Eugenol Ester (AEE)	Paraquat-induced SH-SY5Y	Anti-apoptosis	▪ AEE pre-treatment decreased cell death by increasing the PI3K/Akt signal pathway, reducing the production of apoptotic proteins such as Bax and Bad, and suppressing caspase-3 cleavage	(Zhang et al., 2021b)
Docosahexaenoic Acid and Aspirin	SH-SY5Y	Neuropathology improvement	▪ Activating RXR and PPAR via increased expression of PSD-95, BDNF, and GDNF	(Fu et al., 2017)
Diclofenac	Thapsigargin-induce SH-SY5Y	Anti-apoptosis	▪ Diclofenac inhibits the intrinsic apoptotic pathway, hence suppressing ER-stress-induced cell death	(Yamazaki et al., 2006)
Meloxicam	Fipronil-induce SH-SY5Y	Anti-apoptosis and anti-inflammation	▪ Reducing pro-inflammatory MAPK-mediated factors and preventing p53 translocation from the cytosol to the nucleus	(Park et al., 2015)

Table 2. Anti-inflammatory drugs have effects on Parkinson's disease animal models.

Molecule	Models	Mechanism	Response	References
Meloxicam	Lipopolysaccharide (LPS)-induced male Wistar rats	Anti-inflammation	▪ Reducing LPS-induced Dopaminergic neurodegeneration and decreasing COX-2 activity in activated microglial cells.	(Sui et al., 2009)
Ibuprofen	MPTP-induce male C57Bl mice	Dopaminergic neurons discovery	▪ Reducing DA turnover and COX inhibition, resulting in less ROS production and damage.	(Swiatkiewicz et al., 2013)
Ibuprofen	MPTP-induce male C57Bl mice and LPS-stimulated RAW264.7 cells	Anti-inflammation	▪ Reducing macrophage activation while improving dopaminergic neuron loss. ▪ Ibuprofen and Gagam-Sipjeondaebo-Tang co-administration can lower iNOS, COX-2, IL-1, and IL-6 levels.	(Won et al., 2021)
Celecoxib	Rotenone-induced Sprague-Dawley rats	Antioxidative stress and neuroinflammation	▪ Increasing overall antioxidant capacity and decreasing malondialdehyde in the midbrain protects against rotenone-induced dopaminergic neuron death and histological alterations.	(Sarbishegi et al., 2019)
Aspirin and celecoxib	Electrical lesion-induced PD model	Improving the PD symptoms	▪ Reducing the stiffness in Parkinsonian rats	(Moghaddam et al., 2007)
Aspirin	A53T α-syn transgenic mice	Dopaminergic neuron protection	▪ Boosts DA synthesis in dopaminergic neurons by increasing TH levels	(Rangasamy et al., 2019)
Minocycline	MPTP-induced Male Swiss albino mice	Anti-inflammation	▪ Minocycline provides neuroprotection mostly against parkinsonism caused by a combination of maneb and paraquat. ▪ Reducing M-positive cells	(Dixit et al., 2013)

Flurbiprofen	MPTP-induced male C57BL/6 mice	Anti-inflammation	▪ Decreasing the number of reactive macrophage antigen-1 (Mac-1)-positive microglial cells in the striatum and ventral midbrain ▪ Decreasing the expression of iNOS, Mac-1, and NADPH oxidase (PHOX) ▪ Decreasing the expression of 3-nitrotyrosine, a peroxynitrite fingerprint, in dopaminergic neurons located in SNpc	(L'Episcopo et al., 2010)
Resveratrol	A53T α-synuclein mouse model	Anti-inflammation	▪ Inhibiting α-synuclein aggregation and cytotoxicity, lowering the levels of total α-synuclein and oligomers, reducing neuroinflammation and oxidative stress	(Zhang et al., 2018)

Table 3. The examples of clinical studies of NSAIDs on people with and without PD.

NSAIDs	Patients	Research finding	References
Non-aspirin NSAIDs	44 057 men and 98 845 women free of PD, stroke, or cancer.	▪ Participants who reported regular use of non-aspirin NSAIDs at the beginning of the study had a lower risk of PD than nonregular users during the follow-up.	(Chen et al., 2003)
NSAID	697 078 subjects from the British Columbia Linked Health Database (BCLHD).	▪ Ibuprofen was associated with a lower risk of PD.	(Etminan et al., 2008)
Aspirin, non-aspirin NSAIDs, and acetaminophen	1,931 PD patients who were documented in hospital or outpatient clinic records as having obtained a primary diagnosis of PD; 9,651 controls matched by age and gender from the Danish population registration.	▪ There is no evidence of a protective benefit of non-aspirin NSAID and aspirin prescription medication usage prior to the beginning of Parkinson's disease.	(Etminan et al., 2008)
Aspirin and non-aspirin NSAIDs	22007 male physicians from age 40-84. Individuals without reasons or contraindications for frequent NSAID use and without PD in the baseline.	▪ Participants who had ever used aspirin and non-aspirin NSAIDs had an increased risk of PD.	(Driver et al., 2011)
Diclofenac, ibuprofen and naproxen	7580 PD patients who use NSAIDs.	▪ The use of NSAIDs did not result in a reduction in the occurrence of PD when compared to the control group.	(Brakedal et al., 2021)

Apart from Vitamin C and E, Resveratrol, a polyphenol found in red wine, has been demonstrated to inhibit lipid peroxidation and ROS scavenging. When administered to adult male Sprague-Dawley mice through intraperitoneal injection at a dosage of 30 mg/kg once daily for 7 days, with an additional dose before the operation, Resveratrol resulted in reduced neuronal loss, decreased glial activation, lower levels of matrix metalloproteinase 9 (MMP9), and increased expression of the neuroprotective enzyme HO-1 in the cerebral cortex (Hou et al., 2018).

4.4 Neuroinflammation-targeted nanoparticles

Nanoparticles can be created to target neuroinflammatory areas of the brain specifically. These nanoparticles can be loaded with therapeutic substances such as anti-inflammatory medicines or antioxidants and delivered to the afflicted areas, allowing for localised treatment and reducing off-target effects (Zhu et al., 2021). As carriers for medicinal medicines such as curcumin, okadaic acid, quercetin, anthocyanin, and levodopa, NPs can help treat neuroinflammation. The medications can cross the BBB to target cells more easily with the help of NPs, blocking inflammatory pathways and releasing inflammatory cytokines.

Furthermore, magnetic NPs, such as magnetic iron oxide nanoparticles (IONP), have been used in diagnosis and imaging. Moreover, nanoparticles have anti-

inflammatory properties (Zhu et al., 2021). The current study studied the effects of gold nanoclusters (AuNCs) functionalised with dihydrolipoic acid (DHLA-AuNCs), an antioxidant with documented neuroprotective activities, on the polarisation of BV2. DHLA-AuNCs successfully inhibited pro-inflammatory processes in BV2 cells by generating M2-like polarisation. This was connected with reduced reactive oxygen species and NF-kB signalling, increased cell survival, improved autophagy, and inhibition of apoptosis (Xiao et al., 2020).

4.5 Microglia-specific therapies

Therapies that target microglia, such as small compounds that decrease microglial activation, are now being researched as potential therapies for neuroinflammatory diseases. Considering that the balance of M1/M2 polarisation states of microglia has been involved in the pathological process of neurodegenerative disorders, for example, PD. Some small molecular compounds have been determined for their potential to modulate the balance and interpret the underlying mechanisms (Liu et al., 2019). Farrerol administration increased cell viability in MPP^+-induced BV2 cells by reducing IL-6, IL-1β, and TNF-α levels and reducing NO synthase and COX-2. Farrerol therapy significantly reduced MPP^+-induced TLR4 signalling. TLR4 knockdown reduced the inflammatory response of MPP^+ in BV2 cells (Cui et al., 2019).

The primary saponin extracted from the Chinese plant Platycodonis Radix, Platycodin D (PLD), has anti-inflammatory, anti-allergic, cholesterol-lowering, and neuroprotective effects. The cell viability of MPP^+-induced BV-2 cells was improved by PLD therapy. In MPP^+-treated BV-2 cells, PLD considerably reduced inflammatory mediators such as NO, PGE2, iNOS, and COX-2. PLD inhibited the increased production of inflammatory cytokines TNF-α, IL-1β and IL-6 in MPP^+-treated BV-2 cells. Furthermore, in MPP^+-treated BV-2 cells, PLD reduced the TLR4/MyD88/NF-B pathway activation. TLR4 overexpression abrogated PLD's protective effects in MPP^+-treated BV-2 cells. PLD protected BV-2 cells from MPP^+-induced inflammation by modulating the TLR4-MyD88-NF-B signalling pathway (Sun & Liu, 2020). TAK242, or Resatorvid, is a small molecule inhibitor of the toll-like receptor 4 (TLR4) signalling. TAK-242 specifically targets TLR4 by inhibiting TLR4 signalling (Samarpita et al., 2020).

Rhodobacter sphaeroides lipid A (RSLA) is a 5-acyl chain-containing LA that stimulates horse and hamster immune systems while inhibiting human and mouse immune systems (Anwar et al., 2015). In the previous study, rat co-cultures of neurons and astrocytes were subjected to either 1 µM TAK242 or 0.1 µg/ml RA-LPS for 30 minutes, followed by the addition of α-syn oligomers. The findings indicated that the presence of α-syn oligomers significantly increased ROS levels in BV2 cells. However, this increase was mitigated by the administration of RSLA and TAK242 (Hughes et al., 2019). Immune modulators are used to gather Chimeric Antigen Receptor Treg (CAR-Treg) or Tregs compounds, which are crucial in maintaining tolerance and preventing autoimmune disease. Research is being done on CAR-Treg cell engineering. In gene therapy, CAR-Treg is utilised to inhibit the immune response. On the other hand, the expense of producing a cell-based product is rather significant (Arjomandnejad et al., 2022).

4.6 Stem cell therapies

Stem cell transplantation has shown commitment to reducing neuroinflammation. Stem cells, such as mesenchymal stem cells (MSCs) and neural stem cells (NSCs), can have immunomodulatory effectiveness and release anti-inflammatory chemicals that encourage reduce neuroinflammatory reactions (Lee et al., 2008; Caprnda et al., 2017; Song et al., 2020). Several studies have shown that human umbilical cord mesenchymal stem cells (hucMSCs) can provide neuroprotection. Stem cells communicate with other cells via exosomes (Exos), which are secreted. Exos released by hucMSCs could be efficiently taken up by SH-SY5Y cells after 12 hours of incubation. Exos administration increased the proliferation of 6-OHDA-stimulated SH-SY5Y cells and prevented apoptosis through activating autophagy. Furthermore, Exos crossed the blood-brain barrier (BBB) in vivo and reduced substantia nigra dopaminergic cell loss and death and increased dopamine levels in the striatum. These findings show that hucMSCs-Exos have PD treatment capability and can cross the BBB, highlighting their potential for effective PD treatment (Chen et al., 2020).

The specificity protein 1 (Sp1) transcription factor is a protein that is essential for gene expression regulation. It binds to Sp1 binding sites, which are particular DNA sequences found in the promoter regions of target genes. Sp1 transcription factor is involved in various biological processes such as cell proliferation, differentiation, and death. Exosomes obtained from bone marrow-derived mesenchymal stem cells (BMSC) were treated in MPP^+-treated SH-SY5Y cells and LPS-treated microglia HMC3 cells. BMSC-derived exosomes stimulated cell proliferation and prevented apoptosis of

MPP+-treated SH-SY5Y cells while suppressing inflammatory markers in LPS-treated HMC3 cells. BMSC exosomes reduced neuron loss, damage, and inflammation in a PD animal model induced by MPTP. Thus, BMSC-derived exosomal Gli1 reduces inflammatory damage and neuronal death in vitro and in vivo by decreasing Sp1. These findings lay the groundwork for the prospective clinical application of BMSC-derived exosomes in PD (Cai et al., 2022).

Exosomal transfer into cells (EXOtic) was designed by delivery of the catalase mRNA and implanted in situ in living mice, which could attenuate neuroinflammation. Following 6-OHDA injection into the brain of mice, the results confirmed the attenuation of ROS-induced neuroinflammation by designer exosomes containing the catalase cargo by profiling the expression levels of several markers associated with neuroinflammation in the brain, such as Iba1, TNF-α, and CD11b (Kojima et al., 2018). The therapeutic potential of neural stem cells (NSCs) derived from bone marrow makes them suitable candidates for cellular therapy to repair and regenerate damaged neurons.

In a study involving MPTP-induced C57BL/6 mice, researchers investigated the properties of fasudil, a Rho kinase (ROCK) inhibitor, in combination with NSCs. The results demonstrated that the combination of fasudil and NSCs-protected DA neurons in MPTP-induced PD mice improved the survival of transplanted NSCs in the brain, inhibited the activation and aggregation of microglia in the SNpc and striatum, and also inhibited astrocyte activation (Li et al., 2017).

Glial cell line-derived neurotrophic factor (GDNF), a transforming growth factor beta superfamily member, has been shown to improve motor performance and provide neuroprotection. GDNF's effects on human primary adipose-derived MSCs (hAMSCs) have a promising and encouraging therapeutic efficacy in treating 6-hydroxydopamine-lesioned male C57BL/6 J mice. The results showed significant increases in tyrosine hydroxylase (TH) after transplanting hAMSCs-GDNF into the striatum of lesioned mice (Sun et al., 2020).

4.7 Lifestyle modifications
Certain lifestyle changes, such as regular exercise, proper sleep, and stress management approaches, help reduce neuroinflammation (Madore et al., 2020). Food consumption is also essential. Dietary restriction (DR) is reducing food consumption moderately while avoiding malnutrition. The positive effects of DR on ageing and a

variety of age-related neurodegenerative illnesses, such as PD, are becoming more widely recognised. Fasting has been shown to benefit the brain via metabolic, cellular, and rhythmic mechanisms, which may improve cognitive performance and protect against CNS illnesses.

Furthermore, the DR regimen has been shown to significantly raise the level of BDNF in the striatum, cerebral cortex and hippocampus, and the subsequent activation of BDNF signalling pathways plays an important part in the neuroprotective impact of DR (Wang et al., 2022). DR can influence both central and peripheral variables that contribute to neuroinflammation. Caloric restriction can change the gut microbiota, increase the level of Treg and decrease Th17 in the gut-intestinal tract. Moreover, DR can reduce pro-inflammatory mediators in adipocytes and the brain, including TNF-α and IL-6 (Fontana et al., 2021).

5.0 CONCLUSION
In this article, we highlighted one of the many causes of PD neuroinflammation. Gene mutation and toxic environment are the most common risk factors for PD. These risk factors can cause the accumulation of α-synuclein and oxidative stress in neurons. The accumulation of these molecules can cause protein misfolding, activate glial cells, disturb mitochondrial function, and ultimately lead to cell death. The toxic agents and molecules released from dopaminergic neuron cell death, such as ATP, DAMPs, and α-synuclein, can stimulate the transformation of resting microglia to activated microglia in the form of pro-inflammatory microglia (M1).

M1 microglia play a role in inducing an inflammatory response in the brain, which leads to an increase in cell death and, ultimately, the progression of PD. The major pathways that are linked with the inflammatory response in PD are the NF-κβ, MAPK, and JNK pathways. The M2 phenotype of microglia, on the other hand, can produce different types of anti-inflammatory molecules. Unlike M1 microglia, the main functions of M2 microglia include promoting wound healing, inhibiting inflammation, and restoring homeostasis. An imbalanced distribution of M1 and M2 microglia, especially with a predominance of M1, can lead to the accelerated degeneration of dopaminergic neurons.

Currently, there are several therapeutic approaches for PD: anti-inflammatory medications, neuroprotective agents, antioxidants, neuroinflammation-targeted

nanoparticles, microglia-specific therapies, stem cell therapies, and lifestyle modifications. Receiving treatment enhances patients' mobility, enabling them to engage in a wide range of activities akin to individuals without medical conditions, which, in turn, has a positive impact on the patient's psychological well-being.

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