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Article:

Molecular Mechanisms Underlying Neuroinflammation Intervention with Medicinal Plants: A Critical and Narrative Review of the Current Literature

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Abstract: Background/Objectives: As neurodegenerative diseases become increasingly prevalent, there is a growing interest in natural therapeutic agents to address neuroinflammation, a critical factor in these disorders. With their historical use in traditional medicine, medicinal plants offer the potential for mitigating neuroinflammation. This review aimed to evaluate the effects of medicinal plants on neuroinflammation by conducting a thorough search across reputable databases.

Summary: We reviewed studies that investigated the impact of medicinal plants on neuroinflammation, focusing on effective dosages, mechanisms of action, and clinical implications. We revealed the anti-inflammatory potential of plants such as *Cleistocalyx nervosum* var. *paniala*, *Curcuma longa*, *Cannabis sativa*, and *Dioscorea nipponica*. Although these studies highlight significant anti-inflammatory effects, variability in dosages and phytochemical compositions indicates the need for further research. **Conclusions:** Future studies should emphasize animal models, standardized protocols, and comprehensive safety assessments to facilitate the translation of findings into clinical trials. Additionally, integrating advanced methodologies such as genetic studies and nanomedicine could further enhance these plants' therapeutic potential.

Keywords: Medicinal Plants; Neuroinflammation; Molecular Mechanisms; NF-κB; HO-1; Nrf2

1. Introduction

The increase in life expectancy has been accompanied by a rise in the prevalence of age-related neurodegenerative diseases (NDs). Maintaining neuronal function and cognitive ability depends on the brain's high energy demands, as it is one of the most energetically active organs despite not

performing mechanical work like the skeletal muscles or heart [1-4]. Typically, the human brain consumes approximately 3.5 ml of oxygen per 100 grams of brain tissue per minute [5,6]. This high oxygen consumption makes neurons susceptible to reactive oxygen species (ROS) damage and subsequent inflammation [7-13].

Neuroinflammation is characterized by activating the brain's innate immune system in response to inflammatory stimuli. This response involves the activation of microglia and astrocytes, the release of pro-inflammatory cytokines and chemokines, ROS production, and sometimes the infiltration of peripheral leukocytes into the central nervous system (CNS). While neuroinflammation initially acts as a protective mechanism, sustained or maladaptive inflammation has been identified as a critical factor in the progression of various neurological diseases, including NDs, psychiatric disorders, pain syndromes, stroke, and traumatic brain injury [4,14-19].

Addressing neuroinflammation to reduce disease severity and improve patient outcomes is a promising strategy against neurodegeneration. From a molecular perspective, there are several conventional drug targets for neuroinflammation, such as enzymes, receptors, and ion channels [19-24]. However, the high cost of synthetic drugs presents a challenge, emphasizing the need for alternative approaches [25,26]. This has heightened interest in naturally occurring medicinal plants known for their antioxidant, anti-inflammatory, and neuroprotective properties. These plants are often more cost-effective and have been safely utilized in treatments for thousands of years [27,28].

A substantial body of literature underscores the beneficial effects of dietary phytochemicals and medicinal plants on overall health and longevity [29-32]. Medicinal-plant-based drug discovery remains a vital and underexplored area of research with substantial potential [33]. Despite pharmaceutical advances, plants have historically been a rich source of therapeutic compounds, yet many of their potential benefits are still untapped [34]. By comprehensively investigating these plants, researchers can uncover novel compounds that could offer significant breakthroughs in treating various conditions. Specifically, this approach could lead to the discovery of new treatments for complex issues such as neuroinflammation and neurodegeneration, which are often challenging to address with current therapies [12,35].

Despite previous efforts, existing reviews have yet to fully explore the potential of medicinal plants in regulating neuroinflammation. Tyler et al. [36] offered valuable insights into the therapeutic potential of plants for neurodegenerative diseases. However, their review needed a systematic examination of the literature addressing medicinal plants targeting neuroinflammation. Their focus was broader, with a greater emphasis on ethnobotanical aspects rather than exclusively discussing neuroinflammation. In contrast, Suk et al. [37] explored the regulation of neuroinflammation by herbal medicine and its implications for neurodegenerative diseases. Their review centered predominantly on traditional medicines and their flavonoid derivatives. Additionally, this review, published in 2005, needs to be updated and would benefit from an update incorporating recent advancements in the field. This study aims to fill these gaps by thoroughly reviewing the current literature. The manuscript includes a table (Table 1) that compiles research on medicinal plants' role as potential neuroinflammation modulators. Figure 1 illustrates the microglia's distinct phenotypes, M1 (pro-inflammatory) and M2 (anti-inflammatory).

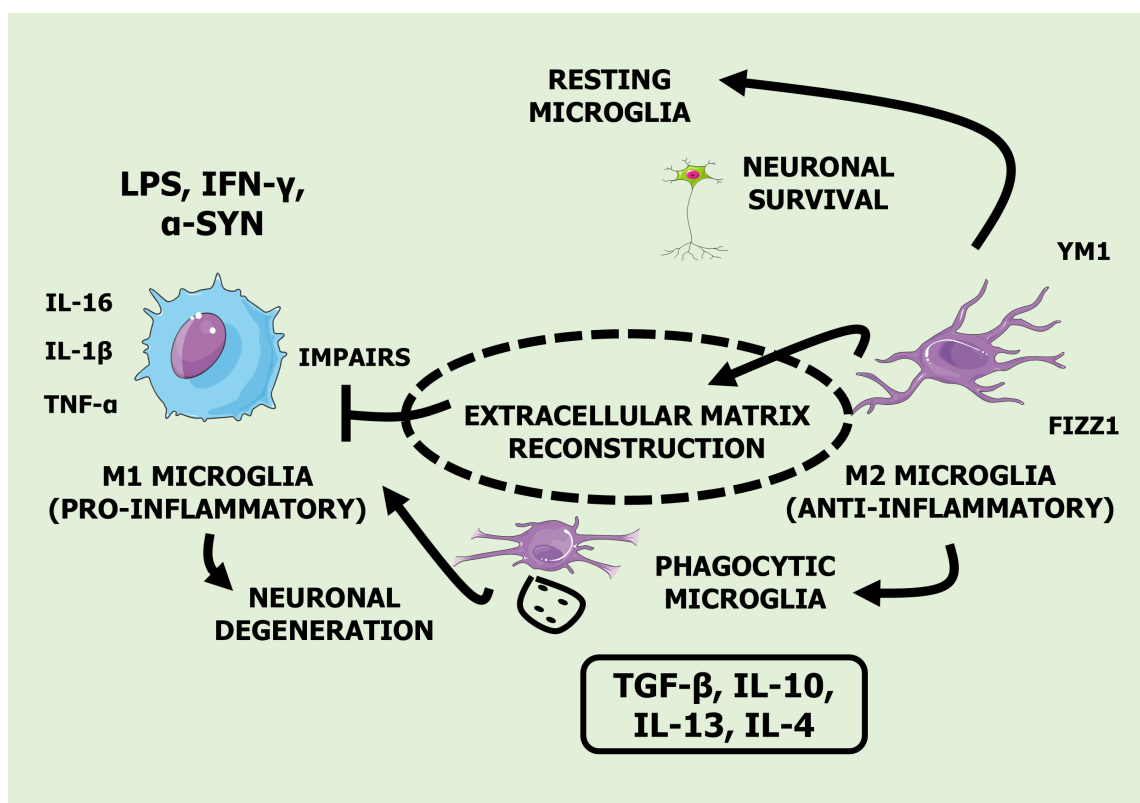


Figure 1. Microglia have M1 and M2 phenotypes depending on conditions. In a homeostatic state, they support neuronal health through synaptic pruning and clearing misfolded proteins. Under stress, they shift to the pro-inflammatory M1 phenotype, releasing reactive oxygen species (ROS) and cytokines that can damage neurons. When exposed to Transforming Growth Factor Beta (TGF-β), Interleukin (IL)-4, IL-10, or IL-13, they switch to the anti-inflammatory M2 phenotype, aiding in phagocytosis, Extracellular Matrix (ECM) rebuilding, and neuronal survival.

Table 1. Medicinal Plants Effects on Neuroinflammation: In Vitro and In Vivo Models, Effective Dosages, Molecular Mechanisms, Clinical Implications, and Study Limitations.

Plants	Models	Interventions	Mechanisms	Clinical Implications	Limitations	Ref
<i>Cleistocalyx nervosum</i> var. <i>paniala</i> (Ferulic acid, aurentiacin, brassitin, ellagic acid, alpinetin and resveratrol)	TNF- α -stimulated BV-2 cells <i>in vitro</i>	5, 10 or 25 μ g/mL CNSE incubated for 24 h <i>in vitro</i>	\downarrow COX-2 activation, \downarrow iNOS function, \downarrow TNF- α , IL-6 and IL-1 β mRNA expression, \downarrow p38MAPK and ERK 1/2 phosphorylation, \downarrow NF- κ B activation, \downarrow p65 and I κ B phosphorylation, \uparrow HO-1 induction (in vitro)	Potential for new anti-inflammatory agents targeting neurodegenerative diseases. Could pave the way for natural, multi-targeted treatments.	Findings are promising but confined to cellular models; lacking animal studies and in-depth safety profiles.	[38]
	LPS-stimulated BV-2 cells <i>in vitro</i>	1, 5, 10, 25, 50 or 100 μ g/mL CNSE incubated for 24 h <i>in vitro</i>	\downarrow NO production, \downarrow iNOS mRNA expression, \downarrow TNF- α , IL-6 and IL-1 β mRNA expression, \downarrow MAPK phosphorylation, \downarrow p-	Could contribute to the development of targeted anti-inflammatory therapies with fewer side effects.	Effects are robust <i>in vitro</i> but lack corroboration in animal models and human trials.	[39]

			JNK, p-ERK 1/2 and p-p38 levels, ↓ NF-κB activation (in vitro)			
<i>Curcuma longa</i> (Curcumin, demethoxycurcumin and bisdemethoxycurcumin)	LPS-stimulated BV-2 cells <i>in vitro</i>	12.5, 25, 50, 100, 150 or 200 μg/mL CLE incubated for 24 h <i>in vitro</i>	↓ NO production, ↓ PGE2 production, ↓ iNOS and COX-2 expression, ↓ TNF-α, IL-6 and IL-1β mRNA expression, ↓ NF-κB activation, ↓ IκB-α phosphorylation and degradation, ↓ p65 nuclear translocation, ↓ MAPK (p38, ERK, and JNK) phosphorylation, ↑ HO-1 expression, ↑ Nrf2 nuclear translocation (in vitro)	Could enhance treatments for neuroinflammation and oxidative stress-related disorders, offering a natural alternative to synthetic drugs.	Effective dosing varies widely, and there is limited evidence of efficacy in diverse populations or clinical settings.	[40]
	LPS-stimulated BV-2 cells <i>in vitro</i> and scopolamine-induced male ICR mice <i>in vivo</i>	1, 10, 50 or 50 μg/mL FCL incubated for 24 h <i>in vitro</i> and 50, 100 and 200 mg/kg FCL <i>in vivo</i>	↓ NO production, ↓ PGE2 production, ↓ iNOS and COX-2 expression, ↑ AP-1 inhibition, ↓ NF-κB activation, ↓ p-MAPKs, ↑ AChE inhibition (in vitro) and ↑ pCREB and BDNF expression (in vivo)	May offer new avenues for treating cognitive deficits and memory impairments associated with neurodegenerative conditions.	Discrepancies between <i>in vitro</i> and <i>in vivo</i> findings highlight a need for more consistent research methodologies.	[41]
<i>Cannabis sativa</i> (Cannabidiol, cannabigerol, cannabidiolic acid, tetrahydrocannabinol, β-caryophyllen, caryophyllene-oxide, α-Humulene and apigenin)	LPS-stimulated BV-2 cells <i>in vitro</i>	1 μg/mL CSE incubated for 24 h <i>in vitro</i>	↓ TNF-α, IL-6 and IL-1β production, ↑ AEA and 2-AG expression, ↓ JNK and p38 activation, ↓ NF-κB nuclear translocation, ↓ ROS production (in vitro)	Could be a cornerstone for novel treatments targeting neuroinflammation and chronic pain, with potential applications in psychiatric and neurological disorders.	Clinical evidence is sparse, and variability in cannabis strains and compounds makes standardization difficult.	[42]
<i>Dioscorea nipponica</i> (Dioscin)	LPS-stimulated BV-2 cells <i>in vitro</i> and scopolamine-	10, 20, 50 or 100 μg/mL dioscin incubated for 24 h <i>in vitro</i> and 60 mg/kg	↓ iNOS and COX-2 expression, ↓ NO and PGE2 production, ↓ TNF-α, IL-6 and IL-1β mRNA expression, ↓ NF-κB nuclear translocation,	May support treatments aimed at improving cognitive functions and mood disorders by targeting	More extensive studies are required to confirm efficacy, dosage safety, and long-term impacts.	[43]

	induced male C57BL mice <i>in vivo</i>	dioscin <i>in vivo</i>	↓ IκB phosphorylation, ↓ p65 nuclear translocation (in vitro) and ↑ BDNF and pCREB expression (in vivo)	neuroinflammatory pathways.		
<i>Centipeda minima</i> (Chlorogenic acid, caffeic acid, rutin, isochlorogenic acid A, isochlorogenic acid B, isochlorogenic acid C and 6-O-angeloylplenolin)	LPS-stimulated BV-2 cells <i>in vitro</i> and LPS-stimulated male C57BL/6J mice <i>in vivo</i>	2, 4 or 6 μg/mL ECM incubated for 24 h <i>in vitro</i> and 100, 200 mg/kg ECM <i>in vivo</i>	↓ NF-κB nuclear translocation, ↓ IκB phosphorylation, ↓ COX-2 and iNOS expression, ↓ NO and PGE2 production, ↓ NOX proteins (in vitro) and ↓ NO, PGE2, TNF-α, IL-6 and IL-1β production, ↓ NF-κB nuclear translocation, ↓ iNOS, COX-2 and NOX2 and NOX4 expression (in vivo)	Potential to develop comprehensive anti-inflammatory therapies targeting multiple pathways involved in neuroinflammation.	Variability in phytochemical compositions can complicate standardization and reproducibility.	[44]
<i>Atractylodis Rhizoma Alba</i> (Atractylenolide I, atractylenolide III, and atractylodin)	LPS-stimulated BV-2 cells <i>in vitro</i>	10, 50, or 100 μg/mL ARAE incubated for 24 h <i>in vitro</i>	↓ NO production, ↓ TNF-α, IL-6 and IL-1β mRNA expression, ↓ iNOS and COX-2 expression, ↑ HO-1 mRNA expression, ↓ NF-κB activity, ↓ MAPK, p38, ERK and JNK activation (in vitro)	May contribute to integrative approaches for treating neuroinflammation and related conditions.	Lack of long-term studies and clinical trials limits understanding of potential side effects and interactions.	[45]
<i>Vaccinium bracteatum</i> (Quercetin, chrysin, apigenin, kaempferol, and lutein)	LPS-stimulated BV-2 cells <i>in vitro</i>	1, 2.5, 5, 10 or 20 μg/ml VBME incubated for 24 h <i>in vitro</i>	↓ NO and PGE2 production, ↓ iNOS and COX-2 expression, ↓ NF-κB p65 nuclear translocation, ↓ TNF-α, IL-6 and IL-1β levels, ↓ ROS production (in vitro)	May inspire new anti-inflammatory and antioxidant treatments with fewer side effects.	Variability in results across different studies and cell models necessitates further investigation.	[46]
<i>Lonicera japonica</i> (Chlorogenic acid, chlorogenic acid, caffeic acid, cryptochlorogenic acid, artichoke, isochlorogenic acid)	LPS-stimulated BV-2 cells <i>in vitro</i>	0.5, 5, 2.5, 5 or 10 μg/mL LJ incubated for 24 h <i>in vitro</i>	↓ NO and PGE2 production, ↓ iNOS and COX-2 mRNA expression, ↓ TNF-α, IL-1β, MCP-1 and MMP-9 production, ↓ ROS levels, ↓ p38 MAPKs, ERK 1/2, JNK and PI3K/Akt phosphorylation, ↓	Could lead to new treatments targeting both neuroinflammation and related oxidative stress.	Complex composition requires more research to determine the most effective components and dosages.	[47]

A, isochlorogenic acid B, isochlorogenic acid C, rutin, hibiscin and loganin)			JAK1/STAT1/3 phosphorylation, ↓ NF-κB nuclear translocation (in vitro)			
<i>Bambusae caulis</i> ((-)-7'-epilyoniresinol 4,9'-di-O-β-D-glucopyranoside (7), (-)-lyoniresinol 4,9'-di-O-β-D-glucopyranoside (8) and bambulignan A)	LPS-stimulated BV-2 cells and glutamate-stimulated hippocampal HT22 cells <i>in vitro</i>	10, 20, 40, 60 or 80 μg/ml BCE incubated for 24 h <i>in vitro</i>	↓ NO, TNF-α, IL-1β and IL-6 levels, ↓ iNOS and COX-2 expression, ↓ ROS production, ↑ HO-1 mRNA expression, ↑ Nrf2 nuclear translocation (in vitro)	Potential for advancing treatments against neuroinflammation and oxidative damage through modulation of key inflammatory and oxidative pathways.	Additional studies required to delineate specific active components and refine therapeutic protocols.	[48]
<i>Zingiberis Rhizoma</i> (Gingerols and shogaol)	LPS-stimulated BV-2 cells <i>in vitro</i>	1, 5 or 10 μg/ml GHE incubated for 24 h <i>in vitro</i>	↓ NO and PGE2 production, ↓ COX-2 mRNA expression, ↓ TNF-α and IL-1β production, ↓ MAPK molecules, ERK1/2, p38 MAPK, and JNK phosphorylation, ↓ NF-κB nuclear translocation (in vitro)	Promising candidate for developing interventions targeting neuroinflammatory processes and related molecular pathways.	Further research is essential to optimize dosing strategies and elucidate mechanistic details.	[49]

Abbreviations: ↑, increase; ↓, Decrease; 2-AG, 2-Arachidonoylglycerol; AChE, Acetylcholinesterase; AEA, Anandamide; AP-1, Activator Protein 1; ARAE, *Atractylodis Rhizoma Alba* Ethanol Extract; BCE, *Bambusae Caulis In Taeniam* Ethyl Acetate; BDNF, Brain-Derived Neurotrophic Factor; CSE, *Cannabis Sativa* Extract; CLE, *Curcuma Longa* Extract; CNSE, *Cleistocalyx Nervosum* Ethanol Seed Extract; COX-2, Cyclooxygenase 2; pCREB, cAMP Response Element Binding protein; ECM, Ethanol Extract of *C. Minima*; ERK, Extracellular Signal-Regulated Kinase; FCL, Fermented *Curcuma Longa*; GHE, Ginger Hexan Extract; HO-1, Heme Oxygenase 1; IL-1β, Interleukin 1β; IL-6, Interleukin 6; iNOS, inducible Nitric Oxide Synthase; Iκba, Nuclear Factor Of Kappa Light Polypeptide Gene Enhancer In B-Cells Inhibitor, Alpha; JAK/STAT, Janus Kinase/Signal Transducer And Activator of Transcription; JNK, C-Jun N-Terminal Kinase; LJ, *Lonicera Japonica*; LPS, Lipopolysaccharide; MAPK, Mitogen-Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein-1; MMP-9, Matrix Metalloproteinase 9; mRNA, messenger Ribonucleic Acid; NO, Nitric Oxide; NOX, NADPH Oxidase; Nrf2, Erythroid-Derived Nuclear Factor; NF-κB, Nuclear Factor Kappa B; PGE2, Prostaglandin E2; PI3K, Phosphatidylinositol 3-Kinase; ROS, Reactive Oxygen Species; TNF-α, Tumor Necrosis Factor-Alpha; VBME, *Vaccinium Bracteatum* Methanol Extract.

2. Nuclear Factor Kappa B (NF-κB): A Central Player in the Development of Neuroinflammation and Neurodegenerative Conditions

In 1986, Sen and Baltimore discovered that, in B lymphocytes, a protein binds to a specific DNA sequence, called NF-κB, that will be acting in case of extensive inflammation [50]. From the moment B cells' maturation induces NF-κB, it is possible to note that this element has fundamental biological importance. As a starting point, it is essential to know that NF-κB is in latency in the cell. With a

stimulus that can be inflammatory, a series of ordered responses begin to occur, and if the problem is resolved, the path of latency returns. In this scenario, the cells of the innate immune system are activated so that they are sufficient to fight minor infections or, in the case of smaller organisms, be their only line of defense. In the case of extensive inflammation, the adaptive immune system cells involve T and B cells. The T cell receptor (TCR) allows T lymphocytes to recognize antigens processed by antigen-presenting cells (APCs), which require the activation of NF- κ B [51,52].

Initially, the most important thing to know is that nuclear factor- κ B (NF- κ B) exists as hetero or homodimers in a family of protein complexes [53]. These dimers make up a family: RelA, RelB, c-Rel, NF- κ B1 (p50), and NF- κ B2 (p52) -transcription factors intrinsically involved with inflammatory processes [54]. The NF- κ B transcription factor has a fundamental role in regulating several aspects through the action of genes, ranging from cell multiplication to multicellular immune and inflammatory responses. For the functions to occur without complications, the NF- κ B system must be adequately regulated, as well as the formation of protein monomers that will form its dimeric family responsible for linking the DNA. [55]. NF- κ B activity is regulated at the mRNA level, so transcriptional signals control this transcription factor [53].

It is essential to know that the cytoplasm is predominantly where NF- κ B is located, so it is inactive as it is in the form of a complex associated with I κ B proteins [56,57]. NF- κ B is responsible for mediating survival factors and an antioxidant cellular response fundamental in microcirculatory disturbance, as it acts on their development [58,59]. However, when oxidative stress happens, NF- κ B translocates to the nucleus from the NF- κ B-I κ B α complex. It is in the nucleus where the initiation of transcription of proinflammatory enzymes - such as COX-2, NADPH oxidase, and sPLA2 - as well as proinflammatory cytokines, like TNF- α , IL-1 β , and IL-6, occurs. [56]

NF- κ B has the property of transcribing genes, which may be proinflammatory, triggering a series of events related to neuroinflammation. [54]. The two catalytic subunits, IKK α and IKK β , and the regulatory subunit NEMO comprise the I κ B kinase complex (IKK) [60]. Two different pathways activate NF- κ B, so the canonical pathway is primarily responsible for inflammation and is stimulated by Toll Like Receptors (TLRs). First, I κ B α captures the p65/p50 dimers in the cytoplasm. Consequently, certain pro-inflammatory stimuli, such as pathogens or cytokines, release p65/p50 dimers through the phosphorylation cascade so that I κ B α is degraded. Soon after, the cognate I κ B motif is linked to the p65/p50 translocated in the nucleus, activating the NF- κ B gene. [54]. The regulatory protein MyD88 (myeloid differentiation primary response 88) mediates the canonical process [60]. In this sense, there is a negative feedback mechanism since the temporary activation of NF- κ B is related to the induction of negative regulators, such as I κ B α , A20, and p105 [61].

The non-canonical NF- κ B pathway has the RelB/p52 as the transcription factor and maintains an intimate relationship with IKK α homodimers, considering that it depends on them to occur. [61]. Interestingly, in certain types of cells, some members of NF- κ B, such as RELA, associate with p100 and are activated through the induction of p100 processing [62]. In this context, regulating this pathway is only possible through the NF- κ B-inducing kinase (NIK) expression. Thus, NIK recruitment to TRAF2 at a steady state is mediated through the TNF receptor-associated factor (TRAF3), resulting in the ubiquitination of NIK and its consequent degradation. Therefore, the NF- κ B complex remains inactive in the cytoplasm due to low levels of endogenous NIK. Upon activation of the non-canonical NF- κ B pathway, TRAF3 proteolysis is induced by TRAF2 – this degradation of TRAF3 releases and accumulates NIK. After this, phosphorylation of p100 by IKK α heterodimers is induced by NIK, promoting an incomplete deterioration that makes p52 available. Ultimately, p52-RelB heterodimers translocate to the nucleus, allowing target genes to be transcribed. [63].

Since the host may be exposed to pathogens that cause tissue damage and infections, inflammation is a protective response of the body capable of promoting the degradation of pathogens and wound healing [62]. In the case of neuroinflammation, the central nervous system promotes an immune response, which is sometimes related to the etiology and course of several psychiatric and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS). In this sense, NF- κ B in the glial cells has a central role in the regulation of chronic

neuroinflammation, that is neurodegenerative [64,65], bearing in mind that various diseases can be exacerbated or intensified in cases of uncontrolled inflammation [66,67].

3. Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2): A Novel Approach to Address Oxidative Stress and Neuroinflammation in Neurodegenerative Disorders

The term oxidative stress was introduced into the literature in 1985 with the publication of a book called "Oxidative Stress", which began a series of studies related to the topic, such as Redox Biology. Several updates, including the action of redox signaling, promoted a redefinition of the initial concept [68]. Firstly, it is essential to understand that oxidative stress is essential for maintaining the organism even at a cellular level. This process is characterized by an imbalance between the production and consumption of oxidative agents, altering homeostasis: on several occasions, the body's ability to neutralize these reactive species decreases, or there is an increase in Reactive Oxygen Species (ROS) production [69,70]. ROS have well-known kinetic, thermodynamic, and physicochemical properties and are produced in a reaction in the mitochondrial chain, encompassing the I and III Complexes, after 4 steps of reduction of 1 electron from an oxygen molecule. In this reaction, the species that are called reactive oxygen species are the 3 primary ones, namely: superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (HO^{\bullet}) [71,72].

It is important to understand that Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), which was discovered in 1994 [73], remains low until the moment when it is induced by an oxidative increase inside the cell, resulting in degradation of this protein and its movement to the nucleus. In principle, Nrf2 is a basic leucine zipper protein (bZIP) that belongs to the cap'n'collar (CNC) family of transcription factors, which also comprises NRF1, NRF3, and p45 NF-E2 and includes 605 amino acids [74-76]. It is interesting to note that Nrf2 exerts protective action against inflammation by inhibiting NF- κ B [77]. In an oxidative stress scenario, Nrf2 is the most important regulator of phase II genes and binds to antioxidant response elements (ARE). Establishing a Keap1/Nrf2 complex in the cytoplasm makes it possible to affirm that the Nrf2/ARE pathway is organized by the negative regulator Kelch-like epichlorohydrin-related proteins (Keap1). Nrf2 phosphorylation is induced through Keap1 so that it forms heterodimers (small musculoaponeurotic fibrosarcoma oncogene homolog, Nrf2-Maf) after being translocated to the nucleus [78-80]. Some pathways indicate that phosphorylation is occurring, and they are the ones that activate Nrf2: PI3K (phosphatidylinositol 3-kinase), CK2 (casein kinase 2), protein kinase C (PKC) and MAP-Ks (protein kinases activated by mitogen) [81]. The control of many antioxidant pathways is carried out through Nrf2 target genes. One can mention, as an antioxidant pathway, the synthesis and regeneration of glutathione (GSH) and the synthesis and recovery of thioredoxin [82].

In its structure, Nrf2 has 7 regions called Nrf2-ECH homology domain (Neh), from Neh1 to Neh7. It is the CNC-bZIP region, surrounded by the Neh1 domain, that makes it possible to bind Nrf2 to DNA, through the dimerization mechanism with small musculoaponeurotic fibrosarcoma (Maf) proteins. The Neh2 domain is responsible for allowing the interaction of Nrf2 with the Keap1 protein, in addition to containing two dragons, DLG and ETGE, of high and low affinity, respectively. Furthermore, for the deterioration of Nrf2 to occur through the action of Keap1-dependent ubiquitin, the role of Neh2 becomes fundamental since the lysine residues present in it participate in the degradation process. The Neh3 domain, positioned at the carboxyl terminus of Nrf2, is responsible for modulating the transcriptional activation of the DNA-binding protein chromo-ATPase helicase (CHD6), which is involved in the transactivation of ARE-dependent genes. In which cAMP (CBP) interacts with the binding protein, transactivation activity involves the Neh4 and Neh5 domains. The Neh6 domain has DSGIS and DSAPGS, which are involved in the β -transducin repeat (β -TrCP), which is a component of proteins that are associated with the negative control of Nrf2 through SCF/ β -TrCP. Finally, the Neh7 domain is related to the retinoic acid receptor α (RAR α), which inhibits the expression of the Nrf2 target gene [83-88].

As previously mentioned, ARE are the sequences present in cytoprotective proteins that are expressed through the induction of compounds that cause oxidative stress linked to Nrf2, so that they represent a fundamental antioxidant in the body. ARE are also called Electrophilic Response Element (EpRE), represented by the following sequence: 5'-gagTcACaGTgAGtCggCAaaatt-3' (capital letters mean essential nucleotides) [87,88]. The ARE pathway has some downstream effectors that are worth highlighting: the detoxification system that includes Phase I (oxidize/reduce), Phase II (conjugation enzymes), and Phase III (drug efflux carriers) [89]. Given the relevance of the ARE, it can be stated that its activation triggers the manifestation of enzymes, such as heme oxygenase 1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO1) [90]. HO-1, in its role as an antioxidant enzyme, is the one that Nrf2 induces most, a fact that guarantees an antioxidant/oxidant balance in the cellular environment in the event of a harmful process [91]. Not only Keap1, but certain other factors, such as histone acetylation, microRNA (miRNA) regulation, and DNA methylation, control the Nrf2/ARE pathway [92].

Given the fact that the Nrf2 pathway is activated mainly as a result of oxidative stress involving ROS and ARE inducers, we can state that these inducers are endogenous (such as NO and H₂O₂), exogenous (such as quercetin and oleanolic acid), therapeutic (such as nimesulide), phytochemicals (such as genistein and curcumin) and environmental agents (e.g. paraquat and some metals) [93,94].

It is also essential to highlight the relevance of Keap1, which has the following functional domains: Kelch or DGR, NTR, CTR, bric-a-brac (BTB), and intervening region (IVR). Through two Kelch domains, Keap1 is established as a homodimer in which each dimer binds to an Nrf2 molecule, with one binding site having high affinity (ETGF motif) and the other having weak affinity (DLG motif). These two motifs are found in the Neh2 domain of Nrf2. It is through the DRG domain that Keap1 and Nrf2 are linked. Furthermore, the E3 ubiquitin ligase complex (Rbx-1) binds to Keap1 through the action of cullin-3, which is an adapter. Because of this process, the 26S proteasome directs Nrf2 to ubiquitination and consequent destruction [74,78,84,95]. It is interesting to note that the manifestation of the target gene occurs as a result of Nrf2 nuclear translocation, and three cysteines residues present in Keap1 (Cys273, Cys151, and Cys288) play a central role in this process [88,96]. Given that Nrf2 is degraded, it is necessary to point out the two ways: Keap1-independent degradation (which occurs in situations of oxidative stress) and homeostatic Keap1-dependent degradation [97]. For the Keap1-independent Nrf2/ARE pathway to be activated, some factors also play a fundamental role, such as AMP-activated protein kinase (AMPK) and protein kinase C (PKC) [98].

When analyzing the relationship between Keap1 and Nrf2, it is possible to state that the most recognized model is the "hinge and latch." In this scenario, there are two reasons at work: ETGE, which, to attach Nrf2 to Keap1, functions as a "hinge," and DLG, which acts as a type of "latch." Combining these two motifs stimulates oxidation, reducing the amount of low-affinity DEG and preventing the ubiquitination of Nrf2 and its consequent degradation. As a result, there is an accumulation of Nrf2, which inserts into the nucleus [98-101]. Throughout the process in which the stress-inducible protein p62 activates Nrf2, the DLG latch is disjointed by inhibitors of the Keap1-Nrf2 relationship [102].

Under conditions of oxidative stress, Nrf2 is neither ubiquitinated nor proteasomal degraded, which results in an abundance of this compound through de novo protein synthesis and consequent deactivation of the E3 ligase adapter activity, promoting the translocation of Nrf2 to the nucleus from the moment its quantity exceeds that of Keap1. Musculoaponeurotic fibrosarcomas (sMaf), such as MafG, MafF, and MafK [103], proteins assemble with Nrf2 to create transcriptionally active heterodimers. In this context, in the promoters of many target genes (involving detoxification enzymes and antioxidants), ARE are identified by the NRF2-sMaf heterodimer [104-106].

Given the relevance of Nrf2 for numerous processes in the body, it is important to highlight its relationship with neuroinflammation and neurodegeneration. Firstly, it is essential to point out that Nrf2 is expressed in the central nervous system (CNS), which involves cells such as microglia and neurons [107]. Microglial cells play a central role in neuroinflammation, and through two distinct activation pathways, they change from the M0 state (resting state) to the M1 or M2 state (activated

state). The M1 state is pro-inflammatory and provides pro-inflammatory cytokines (including tumor necrosis factor- α (TNF- α) and IL-6), increasing the amount of tissue damage through the generation of ROS [66,88,108]. Given this, increased levels of oxidative markers and signaling, in addition to constituent parts of damaged cells, could be seen in patients with diseases such as Parkinson's disease (PD), Multiple sclerosis (MS), and Alzheimer's disease (DA) [76,109]. Therefore, activation of the Nrf2-ARE pathway induces the action of antioxidant proteins and detoxifying enzymes, which defend the body from inflammatory damage [110]. In this scenario, Nrf2 has activators that can neutralize the injuries caused by ROS that promote neurodegeneration [111].

4. Impact of the NLR (Nucleotide-binding Domain and Leucine-rich Repeat Containing) Family Pyrin Domain Containing 3 (NLRP3) Inflammasome on Neuroinflammation: Exploring a Promising Therapeutic Target for Neuroinflammation

Human beings have two forms of immune system defense against pathogens: innate and acquired. In this scenario, some molecules play a central role: pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP). PAMPs are nonspecific microbial molecules that pattern recognition receptors localize and detect, in addition to being fundamental for maintaining the pathogenicity of a group of pathogens. DAMPs can be a molecule, no matter which one, that is exposed during any cell injury or damage process [112-114]. It is interesting to note that mitochondria are responsible for producing energy in the form of ATP by the cell, so that, consequently, they generate reactive oxygen species (ROS). Given that ROS releases cells from damaged mitochondria and this process releases organelles with some damage, it can be assumed that some mitochondrial DAMPs are released extracellularly. In this context, immune system cells are activated by inflammatory activation, releasing more mitochondria and creating a cyclical process that increases inflammation [115].

Furthermore, it is essential to highlight the role of pattern recognition receptors (PRRs), which are responsible for recognizing PAMPs and are distributed both on the cell membrane and in the cytoplasm. Activation of PRRs promotes the generation of pro-inflammatory cytokines and type I interferon (interferon- α and interferon- β), which were stimulated by downstream signaling cascades. The PRRs found in the membrane are mainly formed by Toll-Like receptors (TLRs) and c-type lectin (CLRs). The PRRs, which are in the cytoplasm, are made up, in particular, of the NOD-Like receptors (NLRs), which play a key role in inflammation and are constituted by C-terminal leucine-rich repeats (LRR) and nucleotide-binding domain (NBD/NOD/NACHT) [116-119].

Firstly, it is interesting to understand that, in 2002, Dr. Jurg Tschopp accomplished the brilliant feat of detecting and identifying Pycard/ASC, caspase-1, caspase-5, and NALP1, which are characterized as a complex capable of activating caspases, in addition to the pyrin domain containing 1), which has the function of maturing IL-1 β , creating the concept of inflammasome [120]. In view of this, it is essential to highlight that inflammasomes are an oligomeric and cytosolic multiprotein complex and have the function of acting as mediators in immune responses activated by pathogens or tissue injuries, being activated after the identification of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), in addition to homeostasis-altering molecular processes (HAMPs). In this scenario, the activation of the cysteine protease caspase-1 is coordinated by inflammasomes, so the secretion of the pro-inflammatory cytokines IL-18 and interleukin-1 β (IL-1 β) occurs after proteolytic processing [121-123].

It is necessary to highlight that the best-determined and analyzed inflammasomes are NLRP3 (which contains 3 PYD and is part of the NLR family), NLPR1 (which is also a member of the NLR family and has a leucine-rich repeat of the nucleotide-binding domain), NAIP-NLRC4, pyrin, and AIM2 (which is Absent in Melanoma 2) [124-126].

In this scenario, there are two types of inflammasome: canonical, such as those from the NLR family (NLRP1, NLRP3, NLRC4) and AIM2; and non-canonical ones, which are composed of Malt1, CARD9, Bcl-10, caspase-8, and ASC, and it's commonly dependent on caspase-4 or caspase-5 [122,123,127]. The NLR family has 3 partitions: pyrin domains (PYDs) or an N-terminal caspase

recruitment domain (CARD) and an NOD that is centrally located and surrounded by C-terminal leucine-rich repeats (LRRs) [128].

Following this line of reasoning, the canonical pathway occurs when LRRs are related to the NACHT domain and prevent the generation of inflammasomes when there is no presence of DAMPs and PAMPs stimulation. When PAMPs or DAMPs are identified by LRR, the adapter protein ASC relates to the Pyrin-Pyrin structural domain and is attracted through the NLR protein. After this, the CARD-CARD domain allows the pro-caspase-1 effector domain to join the ASC and overlap into an inflammasome, causing oligomerization and consequent formation of an inflammasome complex that contains a heptamer. Of equal importance, it is necessary to point out the non-canonical inflammasome pathway, which depends on caspase-4/5/11. The transcription of pro-IL-1 β and pro-IL-18 occurs when lipopolysaccharide (LPS) from Gram-negative bacilli is recognized by TLR4, which promotes the activation of NF- κ B. The secretion of pro-caspase-11 is related to this process through the expression of type 1 IFNs caused by Trif/IRF3 [116].

With the advancement of studies on NLRP3, it is essential to highlight that its discovery is linked to its expressions in the immune system, such as in TCD4⁺ and TCD8⁺ cells, and a mild expression in other tissues of the immune system, in the thymus and the lymph nodes, in addition to neurons, myeloid cells, and muscle cells [129,130]. The NLRP3 inflammasome has three components, namely: caspase-1, which is characterized as an effector that promotes the maturation of IL-1 β and IL-18, which are inflammatory cytokines; the NLRP3, which is the intracellular sensor; and the ASC (apoptosis-associated speck-like protein containing a CARD), which is an adapter [131-133]. NLRP3 has three domains, namely: NACHT, the central oligomerization domain, and NOD, the binding domain, which is related to ATPase activity; the amino-terminal pyrin domain (PYD), which is related to protein-protein interaction; and a carboxy-terminal leucine-rich repeat (LRR) domain [134,135].

There are three mechanisms of NLRP3 activation: canonical, non-canonical, and alternative pathways. However, before canonical activation, the NLRP3 inflammasome must be prepared to control the expression of components present in the inflammasome, such as NLRP3 itself, pro-IL-1 β , and procaspase-1 [136]. In the first stage, which is called the priming stage or signal one and requires activation of myeloid differentiation primary response protein (MyD88) [137], certain PAMPs and DAMPs relate to pattern-recognition receptors (PRRs), such as NLRs, NOD, or TLRs. It promotes an intense induction and transcription of NF- κ B, which causes an increase in the expression of the NLRP3 protein. After this, the deubiquitination of NLRP3 and the ubiquitination and phosphorylation of the ASC protein occur, which allows the assembly of the inflammasome. Furthermore, this step is also responsible for inducing post-transductional modifications (PTMs) of NLRP3, which make NLRP3 stable in a state without activity and self-suppressed, but with an appropriate signal [117,131,138-140]. Following the activation step, the NLRP3 oligomer, pro-caspase 1, and ASC are prepared to structure a complex during oligomerization [141]. This phase is known as inflammasome assembly or signal 2, and it is activated by certain molecular and cellular stimuli such as PAMPs, DAMPs, ATP, and ion influx. In this scenario, the pro-inflammatory cytokines IL-18 and IL-1 β and the pyroptosis effector protein, Gasdermin-D (GSDMD), are cleaved by the pro-caspase-1 enzyme so that IL-18 and IL-1 β are released extracellularly after the N-terminal fragments of GSDMD create pores in the plasma membrane. It is also important to point out that ionic and osmotic flow occurs through these pores, and the influx of calcium (Ca²⁺) and efflux of potassium (K⁺) promote cell turgidity so that the influx of Ca²⁺ releases cellular vesicles and the efflux of K⁺ promotes an intensification of inflammasome activation [142-147]. Furthermore, the adaptive immune response is induced by IL-18 and IL-1 β [148]. In humans, caspase-4 triggers the non-canonical response, which occurs as a reaction after Gram-negative bacteria infect the organism [149]. Unlike the previous pathways, in the alternative path, LPS stimulation induces the maturation and consequent secretion of IL-1, in addition to the activation of caspase-1. Furthermore, this pathway requires Syk activity, caspase 4/5, and Ca²⁺ flux influenced by LPS and mediated by CD14/TLR4 [138].

Given the working mechanism of NLRP3, it is possible to state that it has an intrinsic relationship with neuroinflammation and neurodegenerative diseases. The activation of NLRP3

inflammasomes in the central nervous system is related to misfolded proteins and amyloids where, in pathological situations, these proteins have the role of being a signaling molecule that initiates the transcription and expression of NLRP3 and IL-1 β , producing a cascade inflammatory character and positive feedback [150]. Studies have shown that patients with Parkinson's disease (PD) have, in their cerebrospinal fluid (CSF), high concentrations of IL-1 β and IL-18, in addition to upregulated gene expression of caspase-1, ACS, and NLRP3, as well as increased protein expression of IL-1 β , caspase-1 and NLRP3 in cells with only one nucleus in peripheral blood [151,152]. In this sense, the activation of microglial inflammasomes stimulated by α -synuclein and TLR is related to the progression of Parkinson's disease [153,154]. Alzheimer's disease (AD) is also related to the high production of caspase-1, IL-18, and IL-1 β for the activation of NLRP3 inflammasome induced by A β in microglia during the positive feedback loop, which is produced during the systemic neuroinflammation [155-157]. It is interesting to note that a decrease in A β level and an improvement in memory impairment of APP/PS1/NLRP3 $-/-$ mice is related to a knockout of NLRP3 [158]. Therefore, the NLRP3 inflammasome has gained space since its relevance in neurodegenerative and neuroinflammatory diseases gained importance in new research [159-161].

5. JAK/STAT: An Evergreen and Unconventional Pathway in Neuroinflammation and Neurological Dysfunctions

Firstly, it is essential to understand that Janus Kinase or "just another kinase" (JAK) is constituted as a family of transmembrane tyrosine kinases present inside the cell, involving tyrosine kinase 2 (TYK2), JAK1, JAK2 and JAK 3 and, through the action of the Signal Transducers and Activators of Transcription (STAT) pathway, transduce information mediated by, mainly, type I/II cytokines, also phosphorylating signaling molecules carrying Src-Homology 2 (SH2) domains. STATs, which have seven constituents in their family (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6), are characterized as cytoplasmic proteins that, at the end of activation, are recruited and phosphorylated at the C-terminal area in the cytoplasm [162,163]. In this scenario, JAK/STAT has the role of being the pathway responsible for transducing extracellular signals into transcriptional information and adjusting physiological processes [164]. The STAT protein consisting of an N-terminal domain is STAT1, the coiled-coil domain makes up STAT3 and STAT1, the DNA-binding domain forms STAT1, STAT2, and STAT3, Linker is the constituent domain of STAT1 and STAT3, and Src-homology 2 (SH2) that makes up STAT1, STAT3, STAT4, and STAT5a/b, in addition to the C-terminal transcriptional activation domain (TAD), responsible for forming STAT1, STAT2, STAT3, STAT4, STAT5a/b and STAT6 [164].

The fundamental issue to understand about the JAK/STAT pathway is that its regulatory mechanism can be positive and negative. If positive, the following cytokines are involved: growth factors (GFs), interferons (INFs), interleukins, colony-stimulating factors (CSFs), chemokines (CFs), and tumor necrosis factors (TNFs). If the regulation is negative, the protein inhibitors of activated statistics (PIASs), suppressors of cytokine signaling (SOCSs), and protein tyrosine phosphatases (PTPs) are the regulators involved [165,166]. Interestingly, the development of autoimmune diseases is closely related to the suspension of the JAK/STAT signaling pathway, in which the SOCS protein plays an essential role [167,168]. SOCS1 impacts the induction of HLA-DR and CD86 expressions in dendritic cells, so this variant has been characterized as a genetic sign of Multiple Sclerosis [169]. Furthermore, STAT1 and STAT4 act in Th1-type immune reactions in a crucial way, as STAT3 and STAT6 are closely related to Th2 and Th17-type immune responses [170].

More than 50 different cytokines carry out the canonical activation of the JAK/STAT pathway. At its beginning, an extracellular ligand, usually a cytokine, interferon, or growth factor (GF), binds to its receptor, promoting its dimerization. After this, the receptor subunits are targeted and undergo oligomerization, and through the Box1 and Box2 cytokine domains, a homologous area close to the cell membrane joins the region actively functioning in JAK. It is known that numerous activation receptors can bind to a type of JAK, as can be seen in the case of JAK3, which IL-2 and IL-4 activate. JAK phosphorylation is induced by catalyzed tyrosine residues, which also allow the creation of anchoring areas for wandering amino acids. Finally, STAT form homo- and hetero-dimers and

translocate into the nucleus, binding sites that are originated by the activation of JAK, using the SH2 structural domain, resulting in the transcription of different other target genes [171-175]. Then, the tyrosine residues of STAT elements are phosphorylated by JAKs, providing STAT activation [176].

A possible relationship between STAT and inflammation in NK and CD8+ T cells is between the potential response to cytokines and their correspondence with the variable amounts of STAT1 and STAT4, which are determining factors. However, changes in the amount of STAT5 affect the functioning of T cells [177].

The proliferation and activity of cells present in the brain, such as neurons and astrocytes, are regulated by the JAK/STAT pathway. The growth of neural stem cells (NSCs) does not stop during brain development and can be observed in neurogenic areas, including the olfactory bulb's subventricular zone (SVZ). The JAK/STAT pathway regulates NSC growth so that cytokines, especially IL-15, are expressed by adult NSCs in the SVZ, stimulating the action of STAT1, STAT3, and STAT5. Interestingly, blocking JAK prevents NSC multiplication [178].

In this scenario, neurodegenerative diseases are also strictly linked to the JAK/STAT pathway. Alzheimer's disease is related to a dysfunction in the JAK2/STAT3 pathway, in which nicotinic acetylcholine receptors activate this pathway and lower the A β neurotoxicity [179-182]. The pathogenesis of AD was also related to the inactivation of STAT3, in which its activated/phosphorylated configuration (p-STAT3) had a considerable decline in hippocampal neurons of patients with the pathology compared to the control group [183]. Studies have shown that, in mice, high amounts of A β intensify tyrosine phosphorylation and the transcriptional functioning of TYK2, which is related to a high phosphorylation of STAT3 in brains with Alzheimer's disease. Furthermore, when inhibited, JAK/STAT3 signaling blocks microglia and astrocytes' activation in animal neurodegeneration prototypes [184]. The results of Porro et al. demonstrated that inactivation of the JAK/STAT pathway interrupted the amount of secretion of pro-inflammatory cytokines, promoting a rise in the level of IL-4 and IL-10, causing a change in the protective phenotype, attenuating the inflammation present in neurodegeneration [185].

Through the activation of the JAK/STAT pathway, the polarization of pro-inflammatory macrophages becomes possible, having an intrinsic relationship with IFN- γ , so that a deficiency in this interferon, presented by mice, demonstrated a reduction in the amount of neuron loss present in the substantia nigra through the induction of de-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that is also related to the Parkinson's Disease [186]. In their study, Qin et al. [187] demonstrated the relationship between the JAK/STAT pathway in microglial activation, its vital importance in the recruitment of cytokines and chemokines, and its function in Parkinson's disease. In research, possible therapy using a JAK/STAT pathway blockade through the JAK1 and JAK2 inhibitor, AZD1480. The action of α -SYN activated the JAK/STAT pathway in macrophages and microglia, and the role of AZD1480 was to block the major histocompatibility complex Class II, which is induced by α -SYN and, consequently, decreases the activation of STAT1 and STAT3 due to inflammatory gene inhibition in macrophages and microglia. The results showed that therapy with AZD1480 promoted an interruption of neuroinflammation stimulated by α -SYN, preventing microglia activation, the passage of CD4+ T cells and macrophages, and the formation of pro-inflammatory cytokines and chemokines. Notably, in vivo, the JAK/STAT pathway disruption prevented the deterioration of dopaminergic neurons. Therefore, Qin et al. demonstrated the relationship between neuroinflammation and neurodegeneration and the JAK/STAT pathway suppression. In this context, inhibition of the already activated JAK/STAT pathway may be a positive alternative for treating Parkinson's disease [188].

6. Neuroinflammation and Microglial Activation: Charting the Path Forward Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis

At the beginning of the 20th century, the Spanish neuroscientist Pío del Río Hortega identified what he named "microglia," which, at the time, he believed to be a new species of cell present in the brain capable of carrying out phagocytosis. Currently, studies have identified that microglia come from erythro-myeloid progenitors (EMPs), also known as C-KIT⁺/CD41⁺, present in the yolk sac and

multiply from embryonic day 8 (E8) [189]. Microglial cells are constituted as macrophages found in the brain to control neural activity and homeostasis and communicate with other cells of the central nervous system (CNS), such as astrocytes, neurons, and oligodendrocytes [190-192].

It is crucial to understand that between 5 and 10% of cells in the central nervous system (CNS) are microglia, and these have different morphologies that are closely related to their function and the local environment, such as amoeboid, medusa, rod, and branched [193]. It is essential to understand that, in a scenario of damage or injury, microglia begin to have an amoeboid morphology with larger cell bodies and smaller branches [194,195]. Furthermore, microglial cells work with the blood-brain barrier (BBB) to defend the brain against damage and attack pathogens [196].

When installed in the brain, self-renewal is how microglia maintain themselves, requiring the action of transcription factors, such as interferon regulatory factor 8 and PU.1, and cytokines, including colony-stimulating factor (CSF)-1 and interleukin (IL)-34 [197]. For microglia to develop and be preserved, some components are essential, namely extracellular signal-regulated kinases (ERK), which allow the multiplication and maintenance of microglia, and the colony-stimulating factor 1 receptor (CSF1R), which configures as a tyrosine kinase receptor capable of propagating intracellular signals that have a central role in microglial multiplication and CSF-1 activates it and (IL)-34 [198,199]. It is essential to point out that an accelerated depletion of microglia occurs after CSF-1R blockade by pharmacological means [194]. What differentiates microglial cells from macrophages in the adult brain is the fact that microglia are capable of expressing P2RY12/P2RY13, TMEM119, and CD11B, having a low expression of CD45, while circulating macrophages reveal a high expression of CD45 and CD11B [200].

By expressing more than 100 sensory genes, microglia become capable of establishing a link with the microenvironment in which they are located. Among these genes, we can mention complement system receptors, which help them interpret these signals to act as necessary, in addition to Tlr2, P2yr12, and Siglech [201].

There are some mechanisms for regulating microglial activity that play a fundamental role and deserve to be highlighted. Pattern Recognition Receptors (PRRs) are related to regulating innate immunity, recognizing PAMPs and DAMPs. Cytokine receptors are associated with the production of several cytokines, such as transforming growth factor- β (TGF β), tumor necrosis factor- α (TNF α), and interleukins (ILs), since, in the brain, microglia are the largest producer of cytokines. Chemokine receptors are linked to G proteins (GPCRs), called CCL1 receptors (CCR1), CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5. Neurotransmitter receptors participate in the regulation of interactivity between neurons and microglia through the recognition of adenosine triphosphate (ATP) and its metabolites, and it includes cholinergic receptors, glutamate receptors, adrenergic receptors, purinoceptors, and cannabinoid receptors. There is also expression in microglia of myeloid cell receptor-2 (TREM2), which is a receptor present on the surface of cells that is part of the extensive family of Immunoglobulins (Ig) and is triggered through the recognition of pathogens by Toll-like receptors (TLRs), so that TREM2 establishes a relationship with the adapter DNAX-protein-12 activation (DAP12), present in the internal part of the cell. In addition to these receptors, others participate in this regulation, such as phosphatidylserine receptors, scavenger receptors, and Fc receptors [202-205].

Microglial cells are classified by a macrophage-derived system that can sometimes be simplistic: M1 (classical) and M2 (alternative). First, M1, which is activated by interferon-gamma (IFN- γ) and lipopolysaccharide (LPS) and has a pro-inflammatory and neurodegenerative profile, is related to the formation of nitric acid, proteases and pro-inflammatory cytokines ([IL-6], interleukin [IL]-1 β , TNF- α and IL-12) through the expression of NADPH oxidase, that produces inducible nitric oxide synthase (iNOS), and also through the action of the transcription factor signal transducer and activator of transcription 1 (STAT1), which acts via Janus kinase (JAK) 1/JAK2 signaling. In addition, there is also expression of the major histocompatibility complex II (MHC II), the costimulatory molecules CD45 and CD47, integrins such as CD11b and CD11c, and Fc receptors, which can intensify neural injuries and have harmful impacts on neurodegenerative diseases. In the case of M2, with an anti-inflammatory and healing profile, it has the expression of anti-inflammatory cytokines (TGF- β ,

IL-4, IL-10, and IL-13), Th2 recruiting factor CC chemokine ligand 2 (CCL2), arginase 1 (ARG1), CD206 and others. M2 microglia are responsible for generating fibroblast growth factor (FGF), colony-stimulating factor-1 (CSF-1), insulin-like growth factor-1 (IGF-1), in addition to neurotrophic growth factors such as brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF1). In this context, it is interesting to highlight that the "classically activated" M1 phenotype can have its polarization blocked in microglia after a spinal cord injury caused by the deletion of the TMEM16F protein, which acts as an ion channel that depends on Ca²⁺ and phospholipid scramblase [192,206-212]. Interestingly, some microglia, as they synthesize pro-inflammatory and anti-inflammatory markers, have an intermediate phenotype. In this context, IL-4 and IL-13 stimulate M2a-type microglia, which incites CD206, arginase, and chitinase 3-like 3. On the other hand, the M2b phenotype is characterized as an intermediate state of microglia due to the secretion of restorative and inflammatory markers. Furthermore, once the inflammatory issue is resolved, M2c encourages tissue remodeling and repair, forming CD206, transforming growth factor beta (TGF- β) and CD163 [213,214].

Also noteworthy is the ability of microglia to express CD11b, which is also known as a marker "priming", such as MHC-II [215], Transmembrane Protein 119 (TMEM119), Sal-like protein 1 (SALL1), Purinergic Receptor P2Y12 (P2Y12) and Purinergic Receptor P2Y13 (P2Y13), involved in the immune response of the adult brain. Furthermore, it is interesting to note that microglia constantly investigate the CNS to have a relationship with processes such as protein clustering, phagocytosis, secretion of soluble factors, and refinement of the neural circuit. In a scenario of CNS damage, microglia are activated in stages and a complex manner, responding through the action of signaling molecules, such as chemokines and cytokines, to repair the tissue [203,204,216].

It is essential to understand that, to protect the vigilant phenotype of microglia and regulate their activity, the CD200-CD200R and CX3CL1-CX3CR1 axes are vital. However, as a result of aging, there is a reduction in communicability through these axes, a fact that is related to the decrease in the expression of CX3CR1 and the neural ligands CX3CL1 and CD200, creating a pro-inflammatory scenario [201,217,218]. Following this line of reasoning, in the brain of an elderly person, chronic inflammation promotes immunosuppression that damages the distribution pattern of microglia and causes a severe reduction in branching [218]. Interestingly, only in the white matter are the number of microglia positive for MAC-2, which is an indicator of subpopulations of microglia that perform phagocytosis, positively regulated, which does not occur in the gray matter. Therefore, certain elderly people, called "Superagers," had fewer microglia in the cortical white matter and, consequently, had better cognitive function [219].

Alzheimer's disease (AD) is the multifactorial neurodegenerative cause of dementia disease with the highest incidence, and this fact can be observed in the prediction that in the year 2050, in the world, the number of patients with AD will be 139 million [220]. The enzymes beta (β) and gamma (γ)-secretases are responsible for cleaving the amyloid precursor protein (APP), causing the aggregation of amyloid β -peptide (A β) that will not only form A β plaques, but also compacts them and influence their growth, and, from the moment these plaques form in the brain, their strictly close contact with microglia begins, making them reactive [221,222]. In this context, in AD, there is an aggregation of β -amyloid plaques (A β) on the outside of the cell, as well as an accumulation and intraneuronal clustering of hyperphosphorylated tau protein (pTau), which is also called neurofibrillary tangles (NFTs), being that these facts are related to the decrease in the number of neurons and, consequently, in synapses in the cortical and subcortical areas of the brain [223]. In this scenario, through the action of A β , microglia secrete pro-inflammatory cytokines and neurotoxic elements, such as IFN- γ , TNF- α , IL-1, and IL-6, in addition to ROS, so that TNF- α is configured as a of the most relevant cytokines in AD [224]. Moreover, microglial activation in AD has two distinct consequences. The first is related to the clearance and phagocytosis of A β . In contrast, the second, through the kB pathway, promotes the release of many inflammatory mediators, causing neuroinflammatory responses [225]. It is essential to understand that, with genetic studies that recognized more than 25 genetic loci strictly related to the possibility of developing AD, most of the ordinary genetic variants (Sp11, ApoE) or even the uncommon ones (Cd33, Trem2) act by encoding proteins which are mainly

or solely expressed in microglia, so that the transition to disease-associated microglia (DAM) has an intrinsic relationship with these genes and stimulating the receptor expressed on myeloid cells 2 (TREM2) and TYRO protein tyrosine kinase binding protein (TiroBP) [226-228]. According to a study by Rangaraju et al., the DAM has divisions, namely pro-inflammatory, anti-inflammatory, and homeostatic phenotypes. The genes *Cst2*, *CD44*, and *Nampt*, belonging to the pro-inflammatory DAM, were discovered in the human brain proteome, revealing a correlation with AD [229]. It is essential to understand that the secretion of tau protein is carried out by microglia, which intensifies neuronal deterioration, in addition to contributing to the senescence of neighboring microglia, causing an indefinite repetition of these events, which increases the risk of developing AD [230].

Microglia have an intrinsic relationship with AD, as can be analyzed in numerous studies, including that by Sun et al. [231], who observed 1542 genes that were differentially expressed in AD, covering changes characteristic of the state of microglia and AD disease phase, which relate to 12 microglial transcriptional states that have been observed in 443 individuals. By investigating post-mortem brain samples at an advanced age from 217 patients with AD and 226 individuals considered as controls, the transcriptome of 152,459 unique microglial nuclei was analyzed in 6 brain areas. The first step was to collect 174,420 immune cells to perform in silico brain screening of single-nucleus RNA-seq (snRNA-seq) datasets using previously known marker genes (STAR Methods), which formed 16 clusters. Among these, 12 clusters are microglia (0-8 and 10012) and are marked by *CD74*, *CSF1R*, and *C3* so that they were determined as different microglial states based on their molecular signatures and functionalities. The homeostatic microglia (MG0) and its intense expression of homeostatic markers *CX3CR1* and *P2RY12* were subject to annotation and observation, as well as the neuron surveillance microglia (MG1), which has a fierce expression of neurotransmitter receptors, and MG3, which demonstrated great improvement in ribosome biogenesis. Furthermore, three inflammatory states were described (MG2, MG8, and MG10), with an intense expression of both cytokines and cytokine receptors (*IL1B*, *IL4R*, *IL17R*, *IL15*, *IL10RA*, and *CCL3*), which are closely related to immune responses, highlighting signaling through the action of cytokines and the structuring of the inflammatory reaction. From this, the study analyzed 423 individuals considered controls, with early and late AD in the prefrontal cortex, evaluating the statistical significance of the divergences in cellular fractions. It was demonstrated that in AD, MG4, and MG8 presented fractions with a considerable increase, unlike MG1, which presented a decrease in the fraction. Furthermore, using IBA1 pan-macrophage markers used in immunohistochemistry, it was possible to observe that individuals with AD have nuclei that express *P2RY12* with comparatively smaller fractions. With the analysis of the increased expression of *PPARG* evidenced in snRNA-seq data, an increased amount was observed in the fraction of *PPARG*⁺*P2RY12*⁺ cells in AD patients. Linked to this is an enrichment of *FOXP1*⁺*LRRK2*⁺ microglia in this group, demonstrating an MG8 inflammatory state. The discoveries made through in situ hybridization confirm that inflammatory states, together with the state of lipid processing, establish a correlation with diseases.

In the study by Crapser et al. [232], there is a focus on the condensed extracellular matrix (ECM), which is called the perineuronal network, which is linked to the regularization of plasticity in conjunction with astrocytes and synaptic terminals, establishing the modern "tetrapartite synapse." The formation of PNNs occurs mainly around parvalbumin (PV) + GABAergic interneurons present in all brain areas during the process of closing the crucial plasticity interval, allowing a "locking" of proximal synapses and ensuring harmony and preservation synaptic, which happens from the moment in which microglial development is responsible for completing synaptic pruning. After PNN ablation, the reconsolidation and regeneration of remote memories are impaired since memory fragments that were recently formed have the potential to affect the integrity and regeneration of previously assimilated information. In addition, the abnormal functioning of interneurons related to cognitive impairments in AD explains the alteration of the structure of PNNs, which modifies not only the transmission of synapses but also the constitution of the ion channel or neurotransmitter receptor of synapses. In the study, an aggressive sample of the disease was used in mice of the 5xFAD type, and the results were confirmed by a long immunohistochemical (IHC) investigation of human cortical tissue, and, in both, there was essentially a loss of PNNs in the brain. It was also discovered

that 5xFAD brain areas with a high incidence of the disease present an accelerated PNN deficit, and the decrease in the number of PV + interneurons occurs following the impairment of PNN regions and the integrity of the structure. It is essential to highlight that networks that present abnormal morphology in the AD brain are related to microglial activation so that PNN staining demonstrates colocalization in mouse and human microglia. Through the action of the selective colony-stimulating factor 1 receptor (CSF1R) inhibitor PLX5622, the study reveals that the chronic reduction of microglia in the periods following the evolution of the A β plaque in 5xFAD mice, as well as during its progress, prevents, efficiently, the PNN loss. Therefore, it is concluded that the change in microglia due to the disease helps the occurrence of plaque-dependent depletion of PNNs in the human brain and in mice with AD.

A study by Cheng et al. [226] aimed to present the relationship between microglial activation and the expression of protein 2 of the calcium homeostasis modulating family (Calhm2), which is elevated in 5 \times FAD mice, carrying 5 mutations in the AD gene. Firstly, it is essential to point out that intracellular calcium levels are increased by the action of A β , resulting in the activation of the NLRP3 inflammasome in microglia. In this sense, microglial activation is instigated by interferon- γ (IFN- γ) and lipopolysaccharide (LPS), so nicardipine, a calcium channel blocker, inhibits such activation. Furthermore, proteins from the calcium homeostasis modulating family (Calhm, Calhm1, Calhm2 and Calhm3) have gained space in current science. For example, we can observe Calhm1, which has an essential influence on forming A β , calcium homeostasis, and the fragility of neuronal cells that suffer the toxic effects driven by A β . Note also the correspondence between the incidence of AD and the P86L mutation of Calhm1. Linked to this, the study showed increased Calhm2 levels in mice with AD. This protein acts to regulate microglial inflammatory activation and calcium influx, and a decrease in A β deposition, dysfunctions in cognition, and neuroinflammation associated with AD result from both the conventional Calhm2 KO and the microglia-specific KO of Calhm2.

Parhizkar et al. [233] demonstrated that the single ϵ 4 allele of Apolipoprotein E (APOE), as well as the sequential variants in the gene responsible for encoding the stimulatory receptor expressed in myeloid cells 2 (TREM2), have an intrinsic relationship with the probability of developing AD. The importance of Trem2 is widely discussed, including preserving the energetic mechanism, phagocytosis of A β fibrils, uptake of mortar cells, and chemotaxis. This fact can be observed in microglia that react to damage in the brain, in which ApoE and Trem2 are intensely upregulated. ApoE, a prominent component of amyloid plaques, can ensure their clustering and deposition. In the study, APPPS1 transgenic mice were used, with intra-hippocampal injections of brain extracts carrying A β being administered, to compare the results of Trem2 in more mature and A β plaques not experimentally seeded. Small animal positron tomography (μ PET) was also used to produce longitudinal images to verify the process of microglial activation and amyloid depletion. The last step was to observe the loss of Trem2 activity and its relationship with the deposition of ApoE in amyloid plaques in mice and the gathering of microglia, as well as cases of AD in which there is a change in Trem2 coding. In AD situations without TREM2 variants, excessive concentrations of microglia were detected around amyloid plaques. At the same time, a much lower frequency was observed in those AD patients in which TREM2 variants present loss of function, and the microglia that cluster around amyloid plaques promote an increase in ApoE expression. It was recently discovered that those mice that exhibit either a paucity of ApoE or express the p.R47H TREM2 variant, which is related to AD, show a surprising decrease in plaque compaction. Therefore, Parhizkar et al., by demonstrating the action of microglia on amyloid plaque fibrillary, which varies with its activation state, allowed the study to have a high degree of clinical relevance, considering that longitudinal amyloid μ PET catheterizes itself as a readout for amyloid-based therapies.

Other studies have also linked the influence of the ApoE protein with microglial activation and activity, as can be seen in the research by Chernyaeva et al. [234], which demonstrated the interaction between the ApoE protein and the complement regulatory factor H (FH). In this scenario, neurotoxicity and clearance mediated by A β 1-42 are influenced by the specific binding of FH and ApoE, a fact related to the complement activator C1q, which is located in A β brain plaques and related to the pathogenesis of AD.

The study by Meilandt et al. [235], together with the findings of Parhizkar et al. [233], indicates that the functioning of microglia that are dependent on Trem2 can limit plaque formation at an early stage of AD so that, in soluble A β models, this occurs through sequestration and degradation, in addition to an increased occurrence of A β absorption in plaque systems present during the course of the disease. This research investigated the function of Trem2 during microglial activation, neuronal dystrophy in the PS2APP species of β -amyloidosis, and plaque aggregation. Using Campbell-Switzer silver staining, age- and sex-related impacts of Trem2 deletion in excess plaque analyzed were observed in both female PS2APP;Trem2^{ko} and PS2APP;Trem2^{ko} mice. This research investigated the function of Trem2 during microglial activation, neuronal dystrophy in the PS2APP species of β -amyloidosis, and plaque aggregation. Using Campbell-Switzer silver staining, age- and sex-related impacts of Trem2 deletion in excess plaque analyzed were observed in both female PS2APP;Trem2^{ko} mice and female PS2APP;Trem2^{ko} mice. In PS2APP;Trem2^{koA} mice, of all ages and of both sexes, microglial accumulation in the vicinity of the plaque and other forms of activation had an extreme reduction and, as a consequence, the plaques in the brains of these animals presented a more diffuse structure compared to those in PS2APP brains;Trem2^{wt}. This research investigated the function of Trem2 during microglial activation, neuronal dystrophy in the PS2APP species of β -amyloidosis, and plaque aggregation. Using Campbell-Switzer silver staining, age- and sex-related impacts of Trem2 deletion in excess plaque analyzed were observed in both female PS2APP;Trem2^{ko} mice and female PS2APP;Trem2^{ko} mice. In PS2APP;Trem2^{koA} mice, of all ages and both sexes, microglial accumulation in the vicinity of the plaque and other forms of activation had an extreme reduction and, as a consequence, the plaques in the brains of these animals presented a more diffuse structure compared to those in PS2APP;Trem2^{wt} brains. In PS2APP;Trem2^{ko} mice, the depletion of the proximal dendritic column of the plaque was accentuated, a fact that highlighted the relationship between the activation of Trem2-dependent microglia in the surroundings of the plaque and its defending capacity for neurons, differentiating itself from functions interceded by complement and by microglia that cooperate to deplete β -amyloid model synapses. In the study, superior cognitive functionalities in mice with β -amyloid pathology and slowed AD development in humans were related to increased PET signal for TSPO ligands, a "marker of neuroinflammation." The probes used in the clinic (18F-Florbetapir, 11C-PiB) demonstrate stronger labeling than molecular probes (X-34, Thioflavin S and methoxy-X04), which relates to mice with scarce Trem2 and their plaques that cause damage to proximal neurites, a fact that helps clarify the reasons why cognitive reduction correlates more efficiently with the reduction of synapses and tau pathology than with the identification of cerebral amyloid.

Studies by Wang et al. [236] corroborate the influence of TREM2 on AD through the protein tyrosine kinase SYK, demonstrating that the activation of microglia via SYK is not possible using the TREM2R47H variant, present in humans and related to the high probability and development of AD. Furthermore, microglia that exhibit an insufficiency of SYK were found unable to engulf A β plaques, intensifying disease development and behavioral-related damage. A path to immunotherapy was shown in the study, in which, in mice capable of expressing the TREM2R47H allele, an antibody against a receptor that activates SYK, called CLEC7A, was inserted systemically, resulting in possible new options for the treatment of AD.

In their discovery, Qiao et al. [237] highlighted the relationship between a greater probability of developing AD and the p.H157Y variant of TREM2, which is in the cleavage region of it is an extracellular domain and is also considered rare. By generating a new Trem2 H157Y knock-in mouse, using CRISPR/Cas9 technology, the study demonstrated that an improvement in synaptic plasticity and an increase in TREM2 elimination were caused by Trem2 H157Y and, in the existence of amyloid pathology, it was even responsible for increasing the speed of A β clearance, in addition to reducing not only the amyloid load but also dystrophic neurites, the toxic A β oligomer and gliosis in the subsequent phases of amyloid pathology. Therefore, the study demonstrated that Trem2 H157Y may be advantageous for reducing amyloid pathology and its toxicity, in addition to benefiting brain activities, and can negatively control neuroinflammatory pathways related to neurodegeneration.

In the research by Prakash et al. [238], the relationship between lipid droplets (LDs) produced by microglia, which occurs after exposure to A β , and their increase upon the approach of amyloid plaques were studied using the brain of a mouse model with AD 5xFAD and humans with AD. Microglia full of LD showed a deficiency in A β phagocytosis, with the generation of LD being subject to age and disease progression. Through unbiased lipidomic assessment, a considerable reduction in free fatty acids (FFA) was discovered, while long-chain triacylglycerols (TAGs) rose. In this sense, for the conversion of FFAs into TAGs to occur, the enzyme DGAT2 becomes necessary and is also responsible for promoting the generation of LD in microglia. The abundance of the DGAT2 enzyme in the cerebral microglia of patients and brains with 5xFAD is evident in the research, with microglial uptake of A β benefiting after pharmacological inhibition of DGAT2. Considering that lipids, during chronic inflammation as occurs in AD, induce cytotoxicity, it was discovered that such toxic molecules can be metabolized in TAGs by microglia, a type of defense not only for the microglia but also for neurons. Nevertheless, the structure and functioning of microglia are affected by this process. Therefore, the study generates evidence that could lead to a path in which DGAT2 inhibition is characterized as a means capable of boosting the protective characteristic of microglia in AD and other neurodegenerative disorders with abundant protein accumulation and LD deposition.

In the study by Kellogg et al. [239], the major histocompatibility complex I (MHC-I) is related to the regulation of the eradication of synapses linked to the development and pathology of tau in AD, presenting an increased expression during brain aging in mice and humans so that microglia are the origin of both classical MHC-I and non-classical MHC-I. In research, two antigen-independent MHC-I receptors gained prominence: paired immunoglobulin-like receptors type 2 (PILrs) and receptors from the leukocyte immunoglobulin-like receptor subfamily (LILrs). These receptors are induced in microglia in aging and AD processes and have ITIMs (immunoreceptor tyrosine-based inhibition motifs) and ITAMs (immunoreceptor tyrosine-based activation motifs), and, in the recognition cell, both are capable of inciting activation signals. Syc activity, which acts as a regulator of microglial phenotype, is activated by ITAMs and inhibited by ITIMs. The function of Syc, depending on the receptor, can be modulated through the union of Pilr and Lilr receptors with MHC-1, which may include ITIM or ITAM cascades. Through the MHC-I receptors and Pilr and Lilr family receptors found in microglia, MHC-I can control the microglial phenotype together with ITAM, ITIM, and Syc. Kellogg et al. also described a possible activity of microglial MHC-I, that would be related to p16INK4A, a canonical marker of senescence induced in microglia was discovered.

A recent study demonstrated a possible relationship between diet and the risk of developing AD. Velazquez et al. [240] investigated the vitamin nutrient choline, similar to vitamin B, in several foods in the human diet, such as chicken liver, eggs, and milk, and its involvement in the pathogenesis of AD. Choline has the function of donating methyl and preceding the formation of cell membranes, in addition to acting as a precursor of the neurotransmitter acetylcholine, which is reduced in the brain of AD patients and is responsible for putting the α 7 nicotinic acetylcholine receptor (α 7nAChR) into operation, also having the function of an agonist of Sigma-1R (σ 1R). Both receptors act in the CNS, controlling its immune response and, if uncontrolled, favor AD development. Over a while, female APP/PS1 and NonTg mice were fed a choline supplementation (Ch+) (5.0 g/kg choline chloride) or exposed to a controlled amount of choline (1.1 g/kg choline) and evaluated in the Morris water maze using neuropathological and spatial memory tests. Among the results, both a considerable decrease in the β -amyloid plaque burden and an improvement in spatial memory could be observed in APP/PS1 mice. The effects of the research demonstrated reduced amyloidogenic processing of APP, a negative structuring of α 7nACh and σ 1 receptors, and decreases in microglial activation linked to pathology. Therefore, the data found on Ch+ throughout life can bring premises to science, considering its relationship with a possible attenuation of the risk of AD.

Studies on Parkinson's Disease (PD) gained visibility in the scientific community, considering that, in 2020, in the world, more than 9 million individuals lived with the pathology, ranking second as the most common neurodegenerative disease [241,242]. Among the factors that are related to a greater risk of developing PD are advanced age, being male, having a family history of the disease, and even living in a rural area and drinking untreated water [243]. The main symptoms associated

with the disease are apathy [244], pain [245], bradykinesia [246], cognitive impairment, and psychiatric changes [247], in addition to motor impairment, so tremor affects 75% of patients [248,249]. It is essential to understand that some genes are linked to the pathogenesis of PD, such as KAT8 and KANSL1, which are related to mitophagy, and PARKIN and Phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), in which, if presented with mutations, they can be causes of autosomal recessive PD of early origin [250,251]. Other genes, such as leucine-rich repeat kinase 2 (LRRK2) and DJ-1 deglucase protein, in addition to the PINK1 gene already mentioned, control microglial activity in healthy physiological circumstances, which can involve inflammatory processes up to phagocytosis. Mutations in these genes, as occurs in PD, cause an increase in the number of inflammatory markers and, consequently, ROS increase, promoting, on the one hand, an impairment in the function of PINK1 and DJ-1, and, on the other hand, an improvement in the function of LRRK2 and PARKIN [252].

In pathology, dopaminergic neurons, present in the substantia nigra pars compacta (SNpc), degenerate gradually and for a long time, and the filamentous protein α -synuclein (α -Syn) makes up the protein inclusions that are called Lewy bodies [253]. It is essential to understand that α -synuclein can be presented as β -sheet-containing fibrils and plays the secondary role of a seed element for the aggregation of α -synuclein, with self-aggregation being a pathological function. In PD, a decrease in α -synuclein clearance is related to chaperone-mediated macroautophagy and autophagy, favoring the formation of α -synuclein inclusions. In cases where neurons overexpress α -synuclein, exosomes are released, which can provoke a premature reaction from microglia [254,255]. Furthermore, via the activation of inflammasomes, especially NLRP3, the secretion of pro-inflammatory cytokines, such as IL18 and IL1 β , are stimulated by α -Syn aggregates, a fact that establishes a negative correlation with the development of PD [256,257]. α -Syn, in physiological situations, is also responsible for regulating the storage of dopamine in synaptic vesicles and, consequently, establishes a relationship with the expression and functioning of the vesicular monoamine transporter 2 (VMAT2) in neurons in the substantia nigra, corroborating its relationship with PD. In the interaction between α -Syn aggregates and VMAT2, a decrease in dopamine vesicular storage space would lead to a deficiency in synaptic transmission and, as an effect, the death of neurons [257,258].

The importance of α -synuclein (α -syn) and the cell-to-cell transfer of α -syn can be seen in the study by George et al. [259], in which microglia activated by IL-4 or LPS are capable of stimulating aggregation of α -syn, with an increase in the amount of pro-inflammatory cytokines, a fact that is related to the pathogenesis of PD.

It is necessary to point out that an increase in the functioning of the NLRP3 inflammasome causes a deficit in microglial autophagy in PD, leading to a change to a neurotoxic condition in microglia [260]. The study by Yan et al. [261] explored the relationship between the microglial NLRP3 inflammasome, the PARKIN gene, and PD. Through the neuronal expression of NLRP3, PARKIK polyubiquitination occurs and triggers neurodegeneration, so the objective of the research was to understand the function of PARKIK in the activation of NLRP3 using the overexpression of PARKIK in microglia following treatment with lipopolysaccharide (LPS). Three tests were performed on PARKIN knockout mice and wild-type mice to qualify motor activity: open field test, rotarod test, and pole test. It was then discovered that, in LPS-induced mice, the decrease in PARKIN function caused an abundant assembly of microglial NLRP3, contributing to motor deficiency and a reduction in the number of dopaminergic neurons present in the substantia nigra. Therefore, evidence suggests that regulating microglial NLRP3 activation by PARKIN via polyubiquitination ameliorates neurodegeneration in PD.

As previously discussed, Calhm, a membrane protein, played an important role in AD and, for Bo et al. [262], PD also has a relationship with this modulator, which is 1-Methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP)-induced. The research demonstrated that microglial Calhm2 is responsible for, in microglia, modulating the EFhd2-STAT3 pathway, in which EFhd2 is configured as a calcium-binding protein and STAT3 as a protein that, if overactivated, causes the release of pro-inflammatory factors in microglia, resulting in neuronal reduction.

Basurco et al. [263] demonstrated in his study the relationship between innate immune reaction and PD. After the insertion of serotype 9 of the adeno-associated virus, capable of expressing the α -synuclein and mCherry genes, into the substantia nigra, purification of astrocytes (ACSA2⁺) and myeloid cells (CD11b⁺) from both the striatum and midbrain was carried out, to sequence RNA in large volume. CD11b⁺ cells, in models with PD in the midbrain, demonstrated a distinct M2-like anti-inflammatory transcriptomic profile. At the same time, those in the striatum exhibited a pro-inflammatory state comparable to microglia linked to the pathology. The phagocytosis of dopaminergic neuronal bodies in the midbrain was carried out by microglia and infiltrated macrophages, which had increased their quantity. It is interesting to note that astrocytes and microglia presented activation states inherent to the situation throughout the process of α -synuclein-dependent degeneration, with divergent contributions to the inflammatory response and, as a result, highlighted new paths for the treatment of PD through inflammatory response and microglia.

Multiple Sclerosis (MS) is a complex disease of the central nervous system (CNS) that is chronic, neurodegenerative, inflammatory, and autoimmune, which affects more than 2 million people worldwide [264,265]. Although the etiology of the pathology still seems uncertain, some conditions are related to a greater risk of developing MS, including biological sex, genetic constitution, and geographic factors [266]. With advancing age, the degeneration of oligodendrocytes and oligodendrocyte precursor cells increases, which promotes more significant degradation of myelin, a fact that is related to the ongoing neurodegeneration of the pathology, in addition to the fact that the capacity for remyelination is reduced as the years go by years [267]. A large number of receptors are expressed in both macrophages and microglia, such as scavenger receptors (SR), Fc receptors, and complement receptors (CR) so they are related to myelin uptake and act in the pathogenesis of MS [268]. Even in the early stages of the generation of damage in MS, it is possible to observe the activation of microglia, showing a continuous increase in the density of macrophages/microglia as the pathology progresses [269].

Ren et al. [270] demonstrated the relationship between Quaking (Qki), an RNA-binding protein, and the control of phagocytosis carried out by microglia in the process of demyelination and remyelination. The results point to an intensification in the neuroprotective activity of microglia in cases of CNS injuries and neurodegenerative pathologies, such as MS, a fact that is related to more significant phagocytosis by Qki. Therefore, the essential role of microglia in remyelination was confirmed [271]. Moreover, disruption of the blood-brain barrier (BBB) depends on microglial activation. This injury to the BBB is characterized as a recurrent and fundamental aspect of the progression of MS, demonstrated by the study by Yu et al. [272], further highlighting a possible manipulation of microglia to protect the BBB and ensure an improvement in inflammatory demyelination.

7. Exploring Medicinal Plants in Neuroinflammation: Comprehensive Insights on Effects, Dosage, Mechanisms, and Clinical Applications

The studies on various medicinal plants and their phytochemicals present a compelling overview of potential therapeutic agents against neuroinflammation. For instance, the research on *Cleistocalyx nervosum* var. *paniala* indicates that the extract significantly reduces pro-inflammatory markers such as Cyclooxygenase-2 (COX-2) and inducible Nitric Oxide Synthase (iNOS) while inhibiting the activation of Nuclear Factor kappa B (NF- κ B) and its downstream effects. The effective doses, ranging from 5 to 100 μ g/mL, reveal its capability to modulate the inflammatory response in Tumor Necrosis Factor-alpha (TNF- α)- and Lipopolysaccharide (LPS)-stimulated BV-2 cells [38] [39]. These findings underscore the potential of this plant as a source of new anti-inflammatory agents, particularly for neurodegenerative diseases. However, future research should focus on *in vivo* models to corroborate these results and rigorous safety assessments to establish a comprehensive profile in clinical settings.

The efficacy of *Curcuma longa* is well-documented in the context of neuroinflammation, mainly through the action of curcumin and its derivatives. The included studies demonstrated a marked decrease in inflammatory cytokines and a reduction in NF- κ B activation in LPS-stimulated BV-2 cells.

The doses tested ranged from 12.5 to 200 $\mu\text{g}/\text{mL}$, highlighting the potential for *Curcuma longa* as a natural alternative for treating neuroinflammation and oxidative stress-related disorders [40] [41]. Despite its promise, the variability in effective dosing observed across studies indicates a need for more standardized protocols and clinical trials encompassing diverse populations to evaluate its efficacy comprehensively.

Cannabis sativa has garnered attention due to its diverse compounds, including cannabinoids that exhibit anti-inflammatory properties in LPS-stimulated BV-2 cells. The included study indicated significant reductions in pro-inflammatory cytokines while also increasing levels of endogenous cannabinoids, suggesting a dual role in inflammation modulation and pain management [42]. While these findings open avenues for novel treatments targeting neuroinflammation and chronic pain, the study's limitations, such as sparse clinical evidence and the challenges of standardizing cannabis strains, necessitate further research that focuses on specific cannabinoid profiles and their therapeutic implications in clinical settings.

The study on *Dioscorea nipponica* also reveals a promising mechanism for regulating neuroinflammation through the modulation of iNOS and COX-2 expression in both *in vitro* and *in vivo* models. The effective doses were 10 to 100 $\mu\text{g}/\text{mL}$ for *in vitro* studies and 60 mg/kg for *in vivo* applications [43]. Moreover, increased expression of Brain-Derived Neurotrophic Factor (BDNF) and phosphorylated Cyclic AMP Response Element-Binding Protein (pCREB) in animal models indicates potential cognitive benefits. This highlights the need for further research into the long-term effects and safety of *Dioscorea nipponica* and its primary compound, dioscin, particularly regarding their impact on human mood disorders.

Research involving *Centipeda minima* has highlighted its complex phytochemical composition, demonstrating significant anti-inflammatory effects through inhibiting various pathways, including NF- κB and iNOS expression. Li et al. observed a reduction in inflammatory mediators in both *in vitro* and *in vivo* settings, reinforcing its potential to develop comprehensive anti-inflammatory therapies against neuroinflammation [44]. However, the variability in phytochemical compositions underscores the need for future studies that systematically evaluate the contributions of individual components, which would enhance the reproducibility and standardization of therapeutic applications.

Atractylodis Rhizoma Alba has effectively suppressed inflammatory markers in LPS-stimulated BV-2 cells. The mechanisms involved include significant inhibition of NF- κB and Mitogen-Activated Protein Kinase (MAPK) signaling pathways, which are critical in the inflammatory response [45]. The promising results call for integrative approaches in clinical applications. Still, the lack of long-term studies means that further investigations are necessary to determine potential side effects and interactions with other therapeutic agents.

The potential of *Vaccinium bracteatum* in modulating neuroinflammation is also noteworthy, with studies showing significant reductions in pro-inflammatory cytokines and oxidative stress markers. The effective doses ranged from 1 to 20 $\mu\text{g}/\text{mL}$, illustrating its promise as an anti-inflammatory and antioxidant agent [46]. However, variability across studies necessitates additional research to clarify the underlying mechanisms and to confirm its efficacy across different biological models and clinical scenarios. *Lonicera japonica* also exhibits multifaceted anti-inflammatory properties, significantly reducing markers of inflammation *in vitro* [47]. However, the complex composition of this medicinal plant necessitates further exploration into which specific compounds contribute most significantly to its therapeutic effects. Future studies should aim to isolate these components, evaluate their respective contributions to enhancing anti-inflammatory responses, and determine optimal dosages for effective therapeutic outcomes.

In Eom et al.'s study, *Bambusae caulis* demonstrated promising reductions in key inflammatory markers and oxidative stress levels. The observed alterations in Heme Oxygenase-1 (HO-1) and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) signaling pathways suggest that this plant may hold potential for developing new treatments for neuroinflammation [48]. However, the need for additional studies to identify specific active components and optimize therapeutic protocols remains a priority for future research.

Lastly, *Zingiberis Rhizoma* demonstrates substantial anti-inflammatory effects *in vitro* on LPS-stimulated BV-2 cells. The administration of 1, 5, or 10 µg/ml of ginger extract for 24 hours resulted in a marked reduction of Nitric Oxide (NO) and Prostaglandin E2 (PGE2) production, alongside decreased expression of COX-2 messengers Ribonucleic Acid (mRNA). Additionally, the treatment led to lower levels of pro-inflammatory cytokines and downregulated the phosphorylation of MAPK signaling molecules (Extracellular Signal-Regulated Kinase 1 and 2 [ERK1/2], p38 MAPK, and c-Jun N-terminal kinase [JNK]). Notably, there was also a reduction in NF-κB nuclear translocation, highlighting its potential in modulating neuroinflammatory pathways [49]. Given these promising findings, *Zingiberis Rhizoma* may be a valuable candidate for developing neuroinflammation interventions. However, further research is critical to optimize dosing strategies and clarify the underlying mechanisms of action to realize its therapeutic potential.

Overall, while these studies highlight the potential of medicinal plants in regulating neuroinflammation, further research efforts are essential to validate findings across different biological systems, establish optimal dosages, and explore long-term effects in clinical populations. Future research directions could significantly benefit from integrating various advanced methodologies. For instance, genetic studies can be employed to investigate the molecular pathways affected by phytochemicals found in these plants. By utilizing gene expression profiling and Ribonucleic Acid (RNA) sequencing techniques, researchers could elucidate how specific phytochemicals modulate inflammatory pathways at the genomic level, providing insights into their efficacy and mechanism of action.

Immunological assays are also crucial for comprehensively understanding the immune responses elicited by these medicinal plants. Techniques such as flow cytometry and Enzyme-Linked Immunosorbent Assay (ELISA) could quantify cytokine levels and other immune markers in response to treatment with various plant extracts. These essays could help identify the most effective extracts and dosages that reduce neuroinflammation and enhance neuroprotection. Additionally, investigating the immunomodulatory effects of these plants on various immune cell types, including microglia and astrocytes, could reveal how they influence the neuroinflammatory milieu in the CNS.

Molecular docking studies based on plants' phytochemical profiles could also provide valuable insights into their potential interactions with key molecular targets involved in neuroinflammation. Researchers can predict how phytochemicals bind to receptors or enzymes involved in inflammatory pathways by employing computational modeling. Such studies could facilitate the identification of promising compounds for further development and help optimize their structures to enhance efficacy and reduce potential side effects.

Moreover, exploring different extracts, such as aqueous, alcoholic, or supercritical fluid extracts, may reveal varying levels of bioactive compounds and their corresponding effects on neuroinflammation. Comparative studies on the efficacy of these extraction methods could uncover the most effective approaches to maximize the therapeutic potential of medicinal plants. Investigating the influence of specific extraction techniques on the stability and bioavailability of phytochemicals will also be necessary, as this could directly impact their clinical applicability.

Finally, integrating nanomedicine and nanocarriers into the research framework presents an exciting avenue for enhancing the delivery of medicinal plant extracts to treat neuroinflammation. Researchers could improve phytochemicals' solubility, stability, and bioavailability by employing nanoparticles as carriers. Formulating nanocarriers targeting neuroinflammatory sites in the CNS could significantly enhance therapeutic outcomes while minimizing systemic side effects. Furthermore, studies exploring the synergistic effects of combining multiple phytochemicals within nanocarriers could lead to more effective multi-targeted therapies for neuroinflammation.

A multifaceted research approach combining genetic studies, immunological assays, molecular docking, extraction method evaluations, and nanomedicine strategies will advance our understanding of medicinal plants for neuroinflammation. Such efforts can lead to the development of optimized therapeutic protocols that not only leverage the unique properties of each plant but also ensure their safe and practical application in clinical settings. By addressing these areas, future research can provide a more comprehensive understanding of the role of medicinal plants in

mitigating neuroinflammation, ultimately contributing to innovative treatment strategies for related neurological disorders.

9. Conclusions

Exploring medicinal plants in neuroinflammation has yielded promising insights, revealing their potential as valuable therapeutic agents. Studies on *Cleistocalyx nervosum* var. *paniala*, *Curcuma longa*, and *Cannabis sativa* demonstrate their ability to modulate inflammatory pathways and provide symptomatic relief for neurodegenerative conditions. Each plant exhibits unique mechanisms of action, from suppressing pro-inflammatory markers to enhancing neuroprotective factors, underscoring their multifaceted therapeutic potential. Figure 3 illustrates the primary mechanisms by which medicinal plants affect neuroinflammation and associated neuroinflammatory disorders.

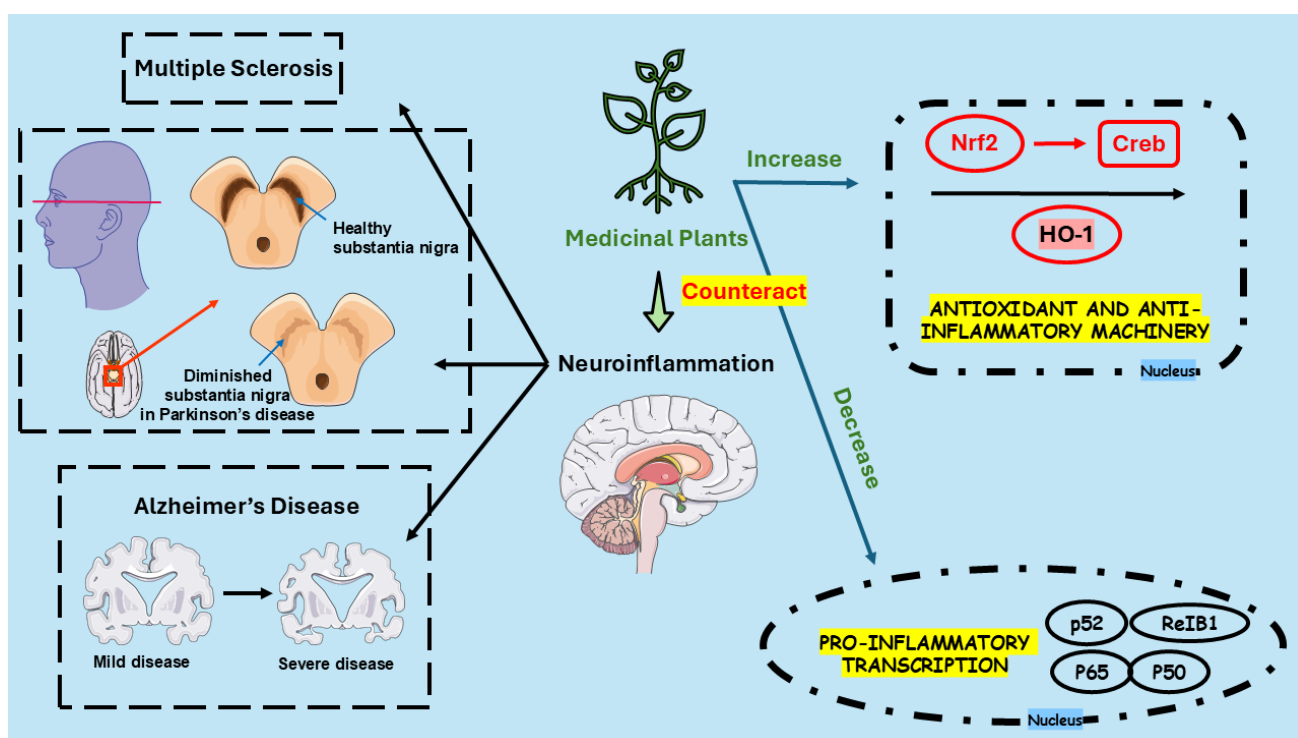


Figure 3. Key Actions of Medicinal Plants in Countering Neuroinflammation and Related Disorders.

Despite these encouraging findings, challenges remain. Variability in effective doses, the need for standardized protocols, and the complexity of phytochemical compositions necessitate further research. Rigorous *in vivo* studies, comprehensive safety assessments, and standardized clinical trials are essential to validate these findings and establish these plants' clinical efficacy and safety profiles.

Future research should integrate personalized medicine approaches, tailoring treatments based on individual genetic, environmental, and lifestyle factors to enhance therapeutic efficacy and minimize adverse effects. Additionally, the principles of green health care—emphasizing sustainability, ecological balance, and the use of natural therapies—should guide the development and application of medicinal plant-based treatments. Employing advanced methodologies, including genetic studies to elucidate molecular pathways, immunological assays to evaluate immune responses, and molecular docking studies to predict interactions with key inflammatory targets, will further advance this field. Optimizing extraction methods and exploring nanomedicine for improved delivery could also enhance the therapeutic potential of these plants. In conclusion, a holistic and multifaceted research approach incorporating personalized medicine and green healthcare principles is crucial for advancing our understanding of medicinal plants in neuroinflammation.

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