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REVIEW

The impact of pharmacological agents on neuroinflammation in neurodegenerative diseases

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Neuroinflammation plays a crucial role in the progression of age-related and chronic neurological diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. This review examines the mechanisms of neuroinflammation by focusing on microglial and astrocyte activation, key signaling pathways such as NFκB and JAK/STAT, and metabolic disturbances that modulate inflammatory processes. Pharmacological treatments, including NSAIDs, minocycline, and statins, have demonstrated some efficacy; however, their therapeutic potential is often limited by suboptimal drug delivery to the target regions and variability in patient response. The review further highlights innovative pharmacologic strategies that modulate microglial function, moving beyond the outdated M1/M2 polarization models and embracing a more dynamic view of microglial plasticity, where activation depends on the local environment and disease context. Furthermore, state-of-the-art computational and experimental drug discovery techniques are leveraged to explore novel therapies. Additionally, natural compounds such as curcumin, resveratrol, and nootropics have shown potential in modulating neuroinflammation through diverse molecular pathways. Compounds were selected based on their demonstrated clinical relevance and ability to modulate neuroinflammation through well-defined molecular mechanisms. Excluded compounds like melatonin and cannabidiol were omitted due to limited clinical data on their efficacy and concerns about off-target effects.

Despite these promising advances, significant challenges remain, particularly in crossing the blood-brain barrier (BBB), which hinders drug bioavailability. Novel strategies, including nanoparticle-based delivery systems, receptor-mediated transcytosis, and focused ultrasound, are being explored to enhance drug bioavailability and cross the blood-brain barrier. Furthermore, the development of reliable biomarkers is essential for tracking treatment response in neurodegenerative diseases. Integrating biomarker-driven therapeutic strategies with emerging drug delivery technologies can lead to more precise, personalized treatment approaches tailored to individual patient needs. These efforts are particularly crucial, as neurodegenerative diseases are heterogeneous in their pathogenesis and progression. Future research should focus on these multidisciplinary approaches to bridge existing gaps in treatment and improve patient outcomes.

Keywords: neuroinflammation, neurodegenerative diseases, pharmacological agents, neuroprotection, inflammatory pathways, therapeutic targets

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Introduction

Various kinds of neurodegenerative diseases are linked with Neuroinflammation, which is a complex and multistage process occurring in central nervous system (CNS) wherein the brain activates immune system [1]. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis and multiple scleroris are common global health problems. Even though these conditions have different etiologies and clinical courses, neuroinflammation likely contributes to the final common pathway of increased neuronal damage resulting in more rapid disease progression. Therefore, in order to establish preventative therapies designed to delay or arrest the progress of neurodegenerative diseases it is crucial that we understand both these mechanisms of disease pathology and explore pharmacological strategies aimed at counteracting them [2].

Background

The activation of glial cells, particularly microglia and astrocytes, is a central event in neuroinflammation, triggered by infections, traumatic injuries, toxic metabolites, and misfolded proteins. Rather than categorizing microglia as M1 or M2, current understanding recognizes that microglial activation spans a continuum of states shaped by disease context and microenvironmental signals. This shift away from the rigid M1/M2 polarization model is supported by recent transcriptomic and functional studies, which demonstrate that microglia exhibit highly plastic, context-dependent phenotypes that cannot be adequately described by binary labels. These activation states are influenced by factors such as local cytokine gradients, metabolic status, age, and disease stage, leading to a diverse array of functional responses ranging from neuroprotection to chronic inflammation [3,4].

In Alzheimer's disease (AD), amyloid-beta (Aβ) plaques trigger microglial activation, leading to the release of inflammatory mediators such as IL-1β, TNF-α, and reactive oxygen species (ROS). Initially, this response may serve a protective role by clearing Aβ deposits, but persistent activation contributes to synaptic dysfunction and neuronal damage [4]. Similarly, in Parkinson's disease (PD), alpha-synuclein aggregates induce microglial responses that involve both neuroprotective and neurotoxic mechanisms, depending on disease progression. In multiple sclerosis

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(MS), a complex interplay between peripheral immune infiltration and resident glial activation results in cycles of demyelination and neurodegeneration [5].

Recent insights emphasize that targeting neuroinflammation requires a nuanced approach that modulates microglial responses rather than simply inhibiting activation. Therapeutic strategies aimed at reprogramming microglial states, such as metabolic rewiring, immune checkpoint modulation, and epigenetic regulation, offer promising avenues for intervention. Understanding the diverse and evolving nature of microglial activation will be essential in designing effective treatments for neurodegenerative diseases [3,5].

This perspective is aligned with the growing body of literature advocating for a spectrum-based classification of microglial phenotypes, as proposed by Paolicelli et al., who emphasized the need for multidimensional frameworks incorporating transcriptional, functional, and spatial data [6].

Rationale

Pharmacological targeting of neuroinflammation presents a promising therapeutic approach, as inflammation plays a well-established role in the progression and exacerbation of neurodegenerative diseases [7]. Current treatment strategies for these conditions primarily focus on symptom management rather than addressing underlying disease mechanisms. However, with growing recognition of the link between neuroinflammation and neuronal degeneration in many CNS disorders, therapeutic strategies aimed at modifying inflammatory function have gained increasing attention for their potential neuroprotective effects [8].

Several pharmacological agents have been investigated for their ability to modulate neuroinflammation, including nonsteroidal anti-inflammatory drugs (NSAIDs) [9], immunomodulatory drugs, and monoclonal antibody therapies. One class of NSAIDs, COX-2 inhibitors, has been shown to reduce levels of pro-inflammatory prostaglandins, which are implicated in neuronal damage, and may even lower the risk of developing Alzheimer's disease [10]. Similarly, monoclonal antibodies targeting key inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), have demonstrated potential in reducing neuroinflammation in preclinical models of neurodegeneration [11].

The selection of these agents is based on their established anti-inflammatory mechanisms and preclinical or clinical evidence suggesting their potential benefits in neurodegenerative diseases. However, other compounds, such as melatonin and cannabidiol, were not included due to insufficient large-scale clinical evidence supporting their efficacy in modulating neuroinflammation. While melatonin has shown promise as an antioxidant and mitochondrial modulator, its direct effects on neuroinflammatory pathways remain inconclusive. Similarly, cannabidiol exerts immunomodulatory effects via CB2 receptor signaling, but variability in dosing, bioavailability, and conflicting trial results have limited its widespread therapeutic consideration. Future studies should further investigate these and other promising compounds to determine their therapeutic viability.

Despite promising findings, translating anti-inflammatory therapies from bench to bedside remains challenging. The complexity and heterogeneity of neuroinflammation—both across and within different neurodegenerative conditions—have contributed to mixed results in clinical trials. This underscores the need for a more precise understanding of neuroinflammatory pathways and the identification of novel therapeutic targets. Additionally, the development of biomarkers to monitor neuroinflammation and assess treatment response in clinical settings is essential for advancing these therapies [12].

Objectives

This review aims to examine the contribution of neuroinflammation to the underlying mechanisms of neurodegenerative diseases and explore potential pharmacological strategies to mitigate its effects. Specifically, this review will:

- Integrate Available Research: Compile and analyze recent studies on neuroinflammation in neurodegenerative diseases, with a focus on the roles of glial cells, cytokines, and other inflammatory mediators in disease progression.
- Identify Gaps in Knowledge: Highlight existing gaps in translational research, particularly the challenges in moving from preclinical models to clinical applications. This includes barriers in drug delivery, regulatory approval, and clinical trial design for pharmacological agents targeting neuroinflammation.
- Establish a Framework for Future Research: Propose new therapeutic targets, combination therapies, and emerging pharmacological agents for neuroinflammation modulation. Additionally, discuss how biomarkers could aid in tracking treatment efficacy and how personalized medicine approaches may enhance patient-specific treatment strategies in neuroinflammation-related diseases.

Discussion

One of the key contributors to neurodegeneration is neuroinflammation [13], a process primarily mediated by glial cells, particularly microglia and astrocytes. These cells play a crucial role in maintaining homeostasis in the central nervous system (CNS) and can exhibit a spectrum of activation states depending on microenvironmental cues. However, in neurodegenerative diseases, glial activation often shifts towards a chronic inflammatory state, leading to excessive release of pro-inflammatory cytokines, oxidative stress, and neuronal damage, thereby exacerbating disease progression.

Understanding the complex and dynamic nature of glial responses in neuroinflammation is crucial for develop-

ing therapeutic strategies that can modulate their activity and mitigate neurodegeneration [14]. Rather than categorizing microglia and astrocytes into rigid pro- or anti-inflammatory states, recent evidence suggests that their activation exists along a continuum, influenced by multiple signaling pathways and disease-specific factors. Targeting these pathways with precision medicine approaches may offer novel therapeutic opportunities to slow disease progression and improve outcomes (Table I).

Microglial Activation

Microglia, the immune-competent cells of the CNS, are primary mediators of neuroinflammatory responses. Under physiological conditions, microglia remain in a surveillant state, exhibiting a highly branched, ramified morphologythat allows continuous monitoring of the CNS environment. In response to injury, infection, or pathological protein accumulation—such as amyloid-beta (Aβ) in Alzheimer's disease (AD) or alpha-synuclein in Parkinson's disease (PD)—microglia become activated, transitioning into an amoeboid morphology and adopting context-dependent functional states [13].

Microglial activation is not binary but exists along a continuum of functional states, ranging from homeostatic and neuroprotective to pro-inflammatory and neurotoxic. Microglia can mediate tissue repair by releasing anti-inflammatory cytokines (e.g., interleukin-10 [IL-10]., transforming growth factor-beta [TGFβ].) and promoting clearance of cellular debris, including misfolded proteins and apoptotic cells [15]. However, in chronic neurodegenerative diseases, microglial activation often becomes dysregulated, leading to sustained inflammation and neuronal damage.

In AD, microglia that cluster around Aβ plaques release pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α]., interleukin-1 beta [IL-1β]., interleukin-6 [IL-6].) along with reactive oxygen species (ROS) and nitric oxide (NO), contributing to oxidative stress, mitochondrial dysfunction, and synaptic loss. Similarly, in PD, microglial activation in response to alpha-synuclein aggregates exacerbates dopaminergic neuron loss, further fueling neuroinflammation. The inability of microglia to effectively transition back to a homeostatic state is considered a key driver of chronic neuroinflammation in neurodegenerative diseases [16].

Astrocyte Activation

Astrocytes, the most abundant glial cells in the CNS, play a crucial role in neuronal support, metabolic regulation, neurotransmitter balance, and maintenance of the blood-brain barrier (BBB). Under normal conditions, astrocytes help modulate synaptic function, regulate cerebral blood flow, and detoxify harmful metabolites. However, in response to CNS injury or neurodegenerative pathology, astrocytes undergo a process known as reactive astrogliosis, characterized by morphological changes and altered gene expression [15].

Reactive astrocytes do not conform to a simple A1 (neurotoxic) vs. A2 (neuroprotective) dichotomy. Instead, their activation states exist on a spectrum, dynamically adapting to local inflammatory cues and disease context. For example, following acute injury (e.g., ischemia or trauma), astrocytes can exhibit pro-repair properties, secreting neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) to support neuronal survival and tissue repair. Additionally, astrocytes assist in clearing apoptotic debris and misfolded proteins, further promoting CNS homeostasis.

However, in chronic neurodegenerative conditions, persistent inflammatory stimuli—particularly microglial-derived cytokines (e.g., IL-1α, TNF-α, and C1q)—can shift astrocytes toward a neurotoxic state. These astrocytes may lose their protective functions and instead release inflammatory mediators that exacerbate synaptic dysfunction and neuronal loss. For instance, in Alzheimer's disease (AD), reactive astrocytes are frequently found surrounding Aβ plaques, contributing to excessive inflammation and neurodegeneration. Similarly, in Parkinson's disease (PD), activated astrocytes have been implicated in dopaminergic neuron degeneration [14].

A key aspect of neuroinflammation-driven pathology is the crosstalk between microglia and astrocytes. Microglial activation can influence astrocyte function, shifting them toward a more inflammatory, neurotoxic phenotype. In turn, astrocyte-derived inflammatory mediators amplify microglial activation, creating a feed-forward loop that sustains chronic neuroinflammation [17]. Understanding these interactions is essential for targeting astrocyte-microglial signaling pathways in future neurodegenerative disease therapies.

Molecular Pathways in Neuroinflammation

NFκB Signaling Pathway

The nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway is a key regulator of immune responses and plays a central role in neuroinflammation. NFκB is a transcription factor that governs the expression of genes associated with inflammation, apoptosis, and cel-

Table I. Disease-Specific Inflammatory Features in Major Neurodegenerative Diseases

Feature	Alzheimer's Disease (AD)	Parkinson's Disease (PD)	Amyotrophic Lateral Sclerosis (ALS)
Primary Aggregated Protein	Amyloid-β, Tau	α-Synuclein	TDP-43, SOD1, FUS
Key Glial Response	Microglial clustering around plaques	Microglial response in substantia nigra	Microglial activation near motor neurons
Dominant Cytokines	IL-1β, TNF-α, IL-6	L-6, TNF-α, IFN-γ	TNF-α, IL-1β, IL-18
Major Pathways Activated	NFκB, NLRP3 inflammasome	NFκB, JAK/STAT	TLR4, NLRP3, NFκB

lular survival. In the central nervous system (CNS), NFκB is predominantly activated in microglia and astrocytes in response to diverse stimuli, including pro-inflammatory cytokines (e.g., TNF-α, IL-1β), oxidative stress, and protein aggregates such as amyloid-beta (Aβ) in Alzheimer's disease (AD) [17].

NFκB activation follows two major pathways:

– Canonical (Classical) NFκB Pathway: Triggered by pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) on glial cells. Cytokine binding to TNF receptors (TNFR) or interleukin receptors (e.g., IL-1R) activates the IκB kinase (IKK) complex, leading to phosphorylation and degradation of IκB (the inhibitory protein that sequesters NFκB in the cytoplasm). Once released, NFκB translocates into the nucleus and binds to promoter regions of inflammatory genes, inducing transcription of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β), chemokines, and adhesion molecules.
– Non-Canonical NFκB Pathway: Activated by B-cell activating factor (BAFF) and CD40 ligand (CD40L). Leads to p100 processing into p52, forming a RelB-p52 complex that regulates chronic inflammatory responses.

NFκB and Chronic Neuroinflammation

Sustained NFκB activation in microglia and astrocytes perpetuates neuroinflammation, creating a cycle of pro-inflammatory cytokine release, neuronal injury, and further glial activation. This contributes to excessive oxidative stress, mitochondrial dysfunction, and synaptic loss, ultimately accelerating disease progression in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [17].

NFκB as a Therapeutic Target

Pharmacological inhibition of NFκB is an emerging therapeutic strategy in neurodegenerative diseases. Several compounds have shown preclinical efficacy:

– Synthetic NFκB inhibitors: Pyrrolidine dithiocarbamate (PDTC): Blocks IκB degradation, reducing TNF-α and IL-1β expression in AD and PD models. Sulfasalazine: Inhibits IKK activation, reducing inflammation in neurodegenerative disease models. BAY 11-7082: Targets IKKβ, suppressing microglial activation.
– Natural compounds with NFκB modulation properties: Curcumin (from turmeric): Reduces oxidative stress and inhibits IKK phosphorylation, indirectly suppressing NFκB activation. Resveratrol (from red grapes): Inhibits NFκB nuclear translocation via SIRT1 activation, promoting an anti-inflammatory microglial phenotype. Celastrol (from Tripterygium wilfordii): Potent NFκB suppressor that reduces neuroinflammatory markers in AD models [18].

Targeting NFκB and its upstream regulators remains a promising therapeutic avenue, but challenges such as blood-brain barrier (BBB) permeability and off-target effects need further investigation.

JAK/STAT Signaling Pathway

The JAK/STAT signaling pathway is a key facilitator of neuroinflammation. Ligand binding to specific receptors at the cell surface engages this pathway, resulting in activation of Janus kinases (JAKs). Upon activation, JAKs phosphorylate signal transducer and activator of transcription (STAT) proteins that subsequently dimerize and translocate to the nucleus, where they regulate genes involved in inflammation, immune response, and cell proliferation [17].

In neuroinflammation, several cytokines—including interferon-gamma (IFN-γ), interleukin-6 (IL-6), and IL-10—activate this pathway, leading to microglial and astrocyte activation. This cascade contributes to the production of pro-inflammatory mediators that drive demyelination and axonal damage. Dysregulation of the JAK/STAT pathway has been implicated in multiple sclerosis (MS), Alzheimer's disease, and other neurodegenerative disorders [16].

Pharmacological modulation of the JAK/STAT pathway represents a promising therapeutic strategy. Among the extensively investigated JAK inhibitors, tofacitinib and ruxolitinib have been selected due to their demonstrated efficacy in reducing neuroinflammation. These inhibitors prevent STAT phosphorylation, thereby suppressing glial activation and cytokine production. Additionally, tofacitinib has shown favorable blood-brain barrier (BBB) permeability, making it a suitable candidate for targeting neuroinflammatory processes. However, BBB penetration remains a challenge for many JAK inhibitors, necessitating alternative drug delivery strategies, such as nanoparticle-based transport or receptor-mediated transcytosis, to enhance CNS bioavailability [19]. A graphical summary of the key mechanisms and therapeutic targets is presented in Figure 1.

Cross-talk Between Neuroinflammation and Metabolic Disorders

The association between neuroinflammation and metabolic disorders, particularly diabetes, is increasingly recognized as a critical contributor to the pathogenesis of chronic neurodegenerative diseases. Chronic metabolic disturbances such as hyperglycemia, insulin resistance, and dyslipidemia promote a systemic pro-inflammatory state, which, in turn, exacerbates neuroinflammation and accelerates neurodegenerative processes.

Type 2 diabetes (T2D) is strongly linked to neurodegeneration, with an approximately twofold increased risk for Alzheimer's disease (AD) and Parkinson's disease (PD). The mechanisms connecting metabolic abnormalities to neuroinflammation are complex. For example, prolonged hyperglycemia leads to the formation of advanced glycation end products (AGEs), which interact with their receptors

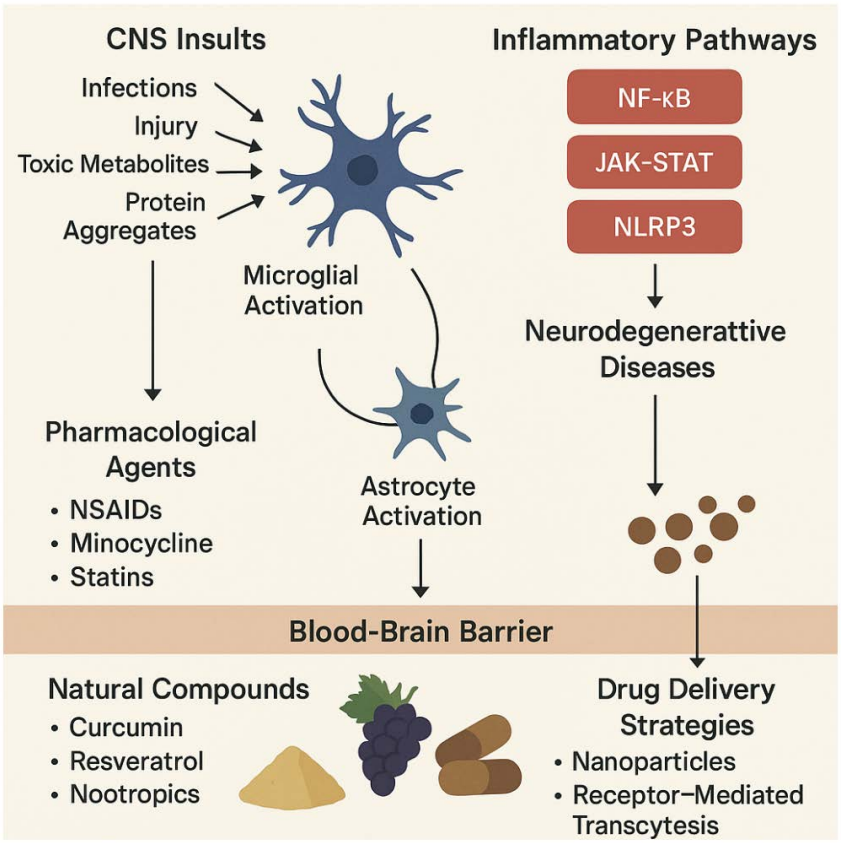

Fig. 1. Graphical abstract illustrating key neuroinflammatory pathways, microglial and astrocyte activation, pharmacological agents (NSAIDs, statins, minocycline), natural compounds (curcumin, resveratrol, EGCG), and novel drug delivery systems across the blood-brain barrier.

(RAGE) on microglia and astrocytes. This interaction activates the NF-κB pathway, resulting in the release of pro-inflammatory cytokines. Similarly, insulin resistance—a hallmark of T2D—disrupts insulin signaling in the brain, reducing glucose uptake and increasing oxidative stress, both of which contribute to neuroinflammation.

Metabolic dysfunction influences neuroinflammation both directly, through the activation of astrocytes and microglia, and indirectly, via systemic immune responses. Obesity, a major risk factor for T2D, promotes the accumulation of adipose tissue macrophages (ATMs), which secrete pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines can cross the blood-brain barrier (BBB) and activate microglia, further amplifying neuroinflammation [17].

Targeting the intersection of metabolic dysfunction and neuroinflammation represents a potential therapeutic approach for neurodegenerative diseases. Metformin, an antidiabetic drug, has shown neuroprotective effects in AD models by activating AMP-activated protein kinase (AMPK) and reducing mitochondrial dysfunction, thereby mitigating neuroinflammation. Similarly, GLP-1 receptor agonists (e.g., liraglutide) exhibit neuroprotective properties by suppressing microglial activation and oxidative stress (Table II).

Pharmacological Agents Targeting Neuroinflammation

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are among the most extensively investigated drug classes in the context of neuroinflammation. Drugs such as aspirin, ibuprofen, and naproxen exert their effects primarily by inhibiting cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which catalyze the conversion of arachidonic acid into pro-inflammatory prostaglandins. Due to their ability to suppress inflammatory responses, NSAIDs have even been proposed as potential prophylactic agents for conditions such as acute respiratory distress syndrome (ARDS).

Table II. Key Signaling Pathways in Neuroinflammation and Their Pharmacological Modulation

Signaling Pathway	Key Components	Pharmacological Modulators	Impact on Neuroinflammation
NFκB Pathway	Pro-inflammatory cytokines (e.g., TNF-α, IL-1β)	Curcumin, Resveratrol, NFκB inhibitors	Reduction in pro-inflammatory cytokine production and oxidative stress
JAK/STAT Pathway	STAT proteins, JAK kinases, cytokine receptors	Tofacitinib, Ruxolitinib	Inhibition of glial activation, reduction in cytokine production
Cross-talk with Metabolic Disorders	AGEs, RAGE, insulin resistance	Metformin, GLP-1 receptor agonists (e.g., Liraglutide)	Reduction of systemic and CNS inflammation, neuroprotective effects

In Alzheimer's disease (AD), NSAIDs have been widely studied for their neuroprotective properties. Epidemiological studies suggest a lower incidence of AD in individuals chronically treated with NSAIDs. The proposed mechanisms include reduced amyloid-beta (Aβ) plaque deposition, inhibition of microglial activation, and suppression of pro-inflammatory cytokine release. For instance, ibuprofen has demonstrated efficacy in animal models of AD by decreasing glial activation and neuroinflammation. Similarly, selective COX-2 inhibitors such as celecoxib have shown potential in preclinical models for reducing neuroinflammation [17].

However, clinical trials in AD patients have yielded inconsistent results. While some studies have reported modest cognitive benefits, others found no significant improvement. One possible explanation is that NSAIDs may be more effective as a preventive measure rather than a treatment for established AD. Moreover, long-term NSAID use carries risks such as gastrointestinal bleeding and cardiovascular complications, limiting their prolonged application in elderly populations.

In Parkinson's disease (PD), NSAIDs have also been investigated for their anti-inflammatory and neuroprotective properties. Similar to AD, their benefits are attributed to inhibition of COX-mediated prostaglandin synthesis and suppression of glial activation. However, clinical studies in PD have not consistently demonstrated a protective effect against disease onset or progression. This underscores the need for further research to determine whether NSAIDs could serve as adjunctive therapies for managing neuroinflammation in neurodegenerative disorders [18].

Minocycline

Minocycline, a broad-spectrum tetracycline antibiotic, has gained attention for its neuroprotective properties, which extend beyond its traditional antimicrobial role. These effects are attributed to its anti-inflammatory and anti-apoptotic actions, distinguishing it from conventional antibiotics. Minocycline modulates neuroinflammation primarily by inhibiting microglial activation, reducing pro-inflammatory cytokine production, and mitigating oxidative stress.

A key mechanism of minocycline involves suppressing microglial activation, which plays a central role in neuroinflammation. Preclinical models of amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) have demonstrated that minocycline reduces pro-inflammatory mediators, including TNF-α, IL-1β, and nitric oxide. Additionally, minocycline inhibits matrix metalloproteinases (MMPs), which contribute to blood-brain barrier (BBB) disruption and neuronal death.

In ALS, minocycline has been explored for its potential to slow disease progression by preserving motor neurons. In rodent models, administration of minocycline at disease onset delayed motor symptom manifestation and extended survival. However, clinical trials have yielded mixed results, with some studies reporting modest benefits while others found no impact on disease progression. Despite these inconsistencies, minocycline continues to be investigated as a potential therapeutic agent for neuroinflammatory disorders [20].

Beyond ALS, minocycline has shown promise in Alzheimer's disease (AD) by reducing Aβ plaque burden, inhibiting microglial activation, and improving cognitive function. In multiple sclerosis, preclinical studies suggest minocycline reduces demyelination and axonal loss via its anti-inflammatory effects. These findings highlight minocycline's potential role in neurodegenerative diseases associated with chronic inflammation.

Statins

Although statins are primarily prescribed for their cholesterol-lowering effects, growing evidence suggests that they modulate neuroinflammation and may have neuroprotective benefits in neurodegenerative diseases. Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, but they also exert pleiotropic effects that extend beyond lipid regulation, including suppression of inflammation, oxidative stress, and immune activation [20].

One key mechanism of statins is their ability to inhibit small GTPase proteins, which are involved in inflammatory signaling pathways. This leads to reduced synthesis of pro-inflammatory cytokines and chemokines while also inhibiting microglial and astrocytic activation. Additionally, statins enhance Apolipoprotein E (ApoE) expression, which facilitates Aβ clearance, a critical process in Alzheimer's disease pathophysiology [22].

Observational studies suggest that statin use may lower the risk of developing AD, and animal studies have demonstrated that statins reduce neuroinflammation and oxidative stress. However, clinical trials evaluating statins in AD have reported mixed results, likely due to variations in study design, patient demographics, and the specific statins tested [22].

In multiple sclerosis (MS), statins have been investigated for their immune-modulating properties. Preclinical research indicates that statins suppress autoreactive T cell activation and reduce pro-inflammatory cytokine production, thereby limiting demyelination and neurodegeneration. Clinical trials assessing statins as adjunctive therapy in MS have reported reductions in brain atrophy and improvements in clinical outcomes [23,24].

Despite their potential benefits in neurodegenerative diseases, concerns remain regarding statin-associated side effects, particularly in older adults. Statins have been linked to myopathy, liver dysfunction, and an increased risk of diabetes, which may limit their long-term use in certain populations [24]. However, given their capacity to regulate neuroinflammation and protect neurons, further research is warranted to explore their integration with other neuroprotective therapies (Table III).

Table III. Dose Ranges of Key Pharmacological Agents in Preclinical and Clinical Studies

Agent	Preclinical Dose (Animal Models)	Clinical Dose (Humans)	BBB Penetration	Translational Notes
Ibuprofen	30–100 mg/kg (oral, mice)	200–800 mg/day	Partial	GI toxicity limits long-term use
Minocycline	25–50 mg/kg (i.p., mice)	100–200 mg/day	High	Well-tolerated, under study in ALS/AD
Simvastatin	5–20 mg/kg (oral, rats)	10–40 mg/day	Moderate	Mixed results in AD; dependent on APOE genotype
Pexidartinib	20–60 mg/kg (oral, mice)	800 mg/day (clinical trial)	Low	Needs novel delivery systems to cross BBB
Curcumin	50–200 mg/kg (oral, rodents)	500–2000 mg/day	Poor	Improved with liposomal/nano-formulations
Resveratrol	10–100 mg/kg (oral, rats)	100–500 mg/day	Moderate	Activates SIRT1; good antioxidant

New Compounds and Natural Products

Targeting Microglial Polarization

Microglia, the resident immune cells of the central nervous system (CNS), play a crucial role in neuroinflammation. They exhibit remarkable plasticity, adopting a spectrum of activation states that are highly dependent on disease context, local cytokine environment, and metabolic cues. These phenotypes range from pro-inflammatory and neurotoxic to anti-inflammatory and neuroprotective roles. In many neurodegenerative diseases, microglial responses become dysregulated and skewed toward persistent pro-inflammatory activation, contributing to chronic inflammation and neuronal injury. Therefore, therapeutically modulating microglial states toward neuroprotective phenotypes represents a promising strategy that moves beyond the outdated binary M1/M2 classification [3, 4].

CSF1R Inhibitors: Pexidartinib (PLX3397)

One emerging pharmacological approach involves targeting the colony-stimulating factor 1 receptor (CSF1R), which regulates microglial survival and proliferation. Pexidartinib (PLX3397), a CSF1R inhibitor, has demonstrated the ability to reduce pro-inflammatory microglia and promote a microenvironment favorable for neuroprotection. Preclinical studies in models of Alzheimer's disease (AD) and other neurodegenerative disorders suggest that Pexidartinib suppresses neuroinflammation, reduces amyloid-beta (Aβ) accumulation, and enhances cognitive function.

Tuftsin-Derived Peptides for Microglial Modulation

Another novel approach is the use of immunomodulatory peptides derived from tuftsin, a naturally occurring tetrapeptide (Thr-Lys-Pro-Arg) involved in immune regulation. These peptides selectively induce the M2 phenotype by interacting with microglial CD11b receptors, leading to: 1. Reduced production of pro-inflammatory mediators (TNF-α, IL-6). 2. Increased secretion of anti-inflammatory cytokines (IL-10, TGF-β). 3. Neuroprotection in models of neurodegeneration.

Given their ability to modulate microglial activation states, tuftsin-based therapies hold promise for treating neuroinflammation-driven diseases, including Alzheimer's disease, multiple sclerosis, and Parkinson's disease (Table IV).

Computational and Experimental Approaches to Drug Discovery

The advent of computational biology and high-throughput screening (HTS) technology has significantly transformed drug discovery, leading to the identification of novel compounds targeting neuroinflammation. Computational methodologies such as molecular docking, machine learning, and in silico screening enable the rapid assessment of large compound libraries, predicting their binding affinity to neuroinflammatory targets such as NF-κB, JAK/STAT, and Toll-like receptor (TLR) pathways, which play a critical role in neurodegenerative diseases.

A notable success achieved through computational approaches is the discovery of small-molecule NLRP3 inhibitors. The NLRP3 inflammasome, a multiprotein complex, facilitates the activation of pro-inflammatory cytokines IL-1β and IL-18, contributing to neuroinflammatory cascades in diseases like Alzheimer's disease (AD) and Parkinson's disease (PD). MCC950, a potent NLRP3 inhibitor identified via computational screening, has demonstrated the ability to reduce neuroinflammation and neuronal loss in preclinical models. However, studies suggest that MCC950 does not significantly impact amyloid plaque accumulation in AD models [26].

In addition to computational strategies, experimental methodologies like CRISPR-Cas9 gene editing are being applied to study neuroinflammatory pathways. By selectively knocking out genes involved in inflammation, researchers can identify novel disease-modifying drug targets. This precise genome-editing tool has been instrumental in elucidating the role of key inflammatory mediators and holds potential for accelerating the discovery of targeted therapeutics for neurodegenerative diseases [27].

Table IV. Comparison of Pharmacological Agents Targeting Neuroinflammation

Pharmacological Agent	Mechanism of Action	Primary Target	Therapeutic Outcomes
NSAIDs	Inhibition of COX enzymes	Prostaglandin synthesis	Reduction of neuroinflammation; mixed results in Alzheimer's disease (AD) clinical trials
Minocycline	Inhibition of microglial activation	Microglia	Delayed disease progression in ALS models; mixed clinical results
Statins	Inhibition of HMG-CoA reductase, reduction of inflammatory pathways	Microglia, Astrocytes	Potential reduction of AD risk; mixed clinical results
Novel Agents (e.g., Pexidartinib)	Targeting microglial polarization (M1 to M2), inhibition of CSF1R signaling	CSF1R	Promising preclinical results, potential cognitive enhancement

Natural Compounds

Anti-Inflammatory Phytochemicals

Plant-derived phytochemicals have gained significant attention for their ability to reduce neuroinflammation and protect against neuronal injury. These natural compounds may serve as alternative or adjunctive therapies for neurodegenerative diseases by targeting multiple inflammatory pathways involved in disease progression.

Curcumin, a polyphenol extracted from turmeric (Curcuma longa), is one of the most extensively studied phytochemicals. It exerts anti-inflammatory effects by suppressing the NF-κB pathway, reducing the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), and inhibiting oxidative stress. Preclinical studies in Alzheimer's disease (AD) models have shown that curcumin attenuates amyloid-beta (Aβ) plaque formation, inhibits microglial activation, and improves cognitive function [28]. However, poor bioavailability has limited its clinical translation. Recent advancements in nanoparticle formulations and liposomal encapsulation have shown promise in enhancing curcumin's bioavailability and therapeutic efficacy [28].

Resveratrol, a polyphenol found in grapes, red wine, and berries, has demonstrated neuroprotective effects by activating sirtuin 1 (SIRT1), a key regulator of stress resistance, mitochondrial biogenesis, and anti-inflammatory gene expression. Studies in neurodegenerative disease models indicate that resveratrol reduces microglial activation, suppresses pro-inflammatory cytokine release, and prevents neuronal loss. Additionally, its strong antioxidant capacity contributes to neuroprotection, making it a promising candidate for treating neurodegenerative disorders.

Epigallocatechin gallate (EGCG), a major polyphenol in green tea (Camellia sinensis), is known for its anti-inflammatory and neuroprotective properties. EGCG inhibits neuroinflammation through multiple signaling pathways, including NF-κB, MAPKs, and JAK/STAT [29]. In preclinical Parkinson's disease (PD) models, EGCG has been shown to reduce dopaminergic neuron loss by suppressing microglial activation and oxidative stress. Additionally, its ability to cross the blood-brain barrier (BBB) enhances its direct action on neuroinflammatory processes, supporting its potential therapeutic application in CNS disorders.

Nootropics as Neuroprotective Agents

Nootropics are compounds that enhance cognitive function and protect against neurodegeneration. In addition to their cognitive-enhancing properties, many nootropics exhibit anti-inflammatory effects, making them potential therapeutic agents for neuroinflammatory diseases [28].

Bacopa monnieri, an Ayurvedic herb traditionally used to treat cognitive disorders, is a well-known herbal nootropic. It contains bioactive compounds, including bacosides, which have been shown to modulate neuroinflammation by reducing pro-inflammatory cytokine production and oxidative stress. Preclinical studies indicate that Bacopa enhances memory and cognitive function in models of neurodegeneration, supporting its potential role in treating Alzheimer's and Parkinson's disease.

Ashwagandha, a medicinal Ayurvedic plant, has gained scientific recognition for its neuroprotective and anti-inflammatory properties. Withanolides, the active constituents of Ashwagandha, have been found to inhibit NF-κB activation, suppress pro-inflammatory cytokine release, and protect against oxidative damage [30]. Animal studies suggest that Ashwagandha improves cognitive function and reduces neuroinflammation, making it a promising natural therapeutic agent for neurodegenerative disorders.

Rhodiola rosea is an adaptogenic herb known for its anti-inflammatory and neuroprotective effects. Its active compounds, rosavins and salidroside, have been shown to modulate stress responses, regulate gene expression, and enhance mitochondrial function. Emerging research suggests that Rhodiola reduces neuroinflammation and oxidative stress, indicating its potential use in the treatment of neuroinflammatory and neurodegenerative diseases [28].

Challenges and Future Directions

A fundamental challenge in treating neurodegenerative diseases is the blood-brain barrier (BBB)—a highly selective interface composed of endothelial tight junctions, pericytes, and astrocytic end-feet. While essential for maintaining CNS homeostasis, the BBB significantly limits the penetration of therapeutic agents, including monoclonal antibodies, cytokine inhibitors, and small-molecule anti-inflammatory drugs. This limitation contributes to the suboptimal efficacy of treatments for conditions like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

Since only small, lipophilic molecules can passively diffuse across the BBB, researchers are actively developing novel drug delivery strategies to bypass or modulate BBB permeability. These include:

- Nanoparticle-based carriers: Liposomes and polymeric nanoparticles facilitate targeted transport via receptor-mediated transcytosis, with preclinical studies demonstrating improved CNS delivery of anti-inflammatory agents in AD and PD models. For example, nanoparticle-encapsulated curcumin has been shown to enhance amyloid-beta clearance in AD.
- Focused ultrasound (FUS)-mediated BBB disruption: Temporarily increases BBB permeability, enabling enhanced uptake of therapeutic agents like beta-secretase inhibitors in AD trials. Recent studies indicate that FUS improves the delivery of monoclonal antibodies targeting amyloid plaques.
- Molecular modifications: Prodrugs and lipid-conjugated molecules enhance lipophilicity to improve CNS penetration, as seen in L-DOPA derivatives for PD. Additionally, glycosylation modifications have been used to improve the CNS uptake of anti-inflammatory drugs.

– Intranasal drug delivery: Bypasses the BBB via the olfactory and trigeminal nerve pathways, an approach being explored for insulin-based AD therapies. This method has shown promise in delivering neurotrophic factors for PD.

Notably, BBB integrity itself is compromised in many neurodegenerative diseases, influencing both drug penetration and therapeutic outcomes. In AD, BBB dysfunction is characterized by disrupted tight junctions and pericyte loss, leading to increased permeability and impaired clearance of amyloid-beta peptides, which may paradoxically hinder drug efficacy. Similarly, PD involves alterations in P-glycoprotein function, reducing the clearance of neurotoxic compounds and potentially modifying drug pharmacokinetics. In ALS, vascular endothelial dysfunction has been associated with increased permeability, which could either facilitate drug entry or increase the risk of neurotoxicity.

Thus, optimizing BBB-targeted delivery requires a balance between increasing CNS drug penetration while minimizing systemic side effects. Future research must refine these approaches through patient-specific biomarker assessments, improving the precision of drug delivery strategies in neurodegenerative diseases. Incorporating advanced imaging modalities such as dynamic contrast-enhanced MRI may further aid in real-time assessment of BBB permeability and guide personalized treatment strategies.

Biomarkers and Diagnostics

The complexity and heterogeneity of neuroinflammatory processes, particularly at the systemic level, highlight the urgent need for reliable biomarkers to assess drug efficacy, disease onset, and progression in neurodegenerative disorders. Biomarkers provide crucial insights into molecular pathways, enabling accurate diagnosis, prognosis, and treatment monitoring. However, the identification of clinically meaningful biomarkers for neurodegenerative diseases remains a challenge [31].

Current Biomarkers in Neurodegenerative Diseases

Currently, the most established biomarkers for neurodegenerative diseases are cerebrospinal fluid (CSF) measurements of amyloid-beta (Aβ) and tau proteins, which have been validated for Alzheimer's disease (AD) diagnosis [32]. Similarly, CSF levels of alpha-synuclein have shown high sensitivity for diagnosing Parkinson's disease (PD) [4]. However, these biomarkers are not neuroinflammation-specific and do not assess functional changes related to anti-inflammatory treatments.

Emerging Biomarkers for Neuroinflammation

Novel biomarkers reflecting neuroinflammation include:

– Pro-inflammatory cytokines (e.g., IL-1β, TNF-α) in CSF and blood, which indicate immune system activation.
– Soluble microglial markers (e.g., sTREM2), associated with microglial activation and neurodegenerative progression.
– Positron emission tomography (PET) tracers, such as those binding to translocator protein (TSPO), which provide in vivo imaging of neuroinflammation.
– While these biomarkers hold promise, they lack large-scale validation in heterogeneous patient populations and are not yet widely implemented in clinical practice [33].

Challenges in Biomarker Development

The dynamic nature of neuroinflammation makes biomarker standardization difficult, as inflammatory responses vary between individuals and fluctuate over time. To address this, longitudinal studies are essential to identify predictive biomarkers that can track disease progression and therapeutic responses.

Future advancements may involve combining biomarker data with neuroimaging modalities, such as functional MRI (fMRI) and PET, to enhance real-time monitoring of neuroinflammation and assess drug efficacy dynamically. However, these techniques are cost-intensive and not universally accessible, underscoring the need for non-invasive, cost-effective biomarker strategies to enable wider clinical application.

Personalized Medicine: The Importance of Patient-Specific Approaches

Personalized medicine is emerging as a crucial approach in addressing neurodegenerative diseases, given their heterogeneous nature in both pathophysiology and progression. While these disorders share common molecular and genetic mechanisms, their clinical manifestations differ significantly, making a one-size-fits-all treatment approach ineffective. Instead, personalized medicine focuses on tailoring interventions based on individual patient profiles, including genetic predisposition, disease subtype, and specific inflammatory pathways, to optimize therapeutic outcomes while minimizing adverse effects [32].

A key aspect of personalized treatment strategies for neuroinflammation involves identifying precision biomarkers that reveal active immune pathways in each individual. These biomarkers help determine the most effective pharmacological agents that target specific inflammatory mediators, such as cytokines and immune cell signaling pathways. Advances in genomic and transcriptomic analysis have made it possible to detect patient-specific variations, including mutations in immune regulatory genes and differential cytokine expression patterns, which influence disease progression and response to treatment [32]. By leveraging these molecular insights, therapies can be tailored to address the underlying immune dysfunction in each patient.

Artificial intelligence and machine learning are playing an increasing role in personalized medicine by analyzing

vast datasets of genomic, metabolic, and biomarker information. These technologies facilitate real-time tracking of disease progression and treatment response, allowing for dynamic modifications to therapeutic regimens [31]. AI-driven models enhance clinical decision-making by predicting treatment efficacy, identifying responders to specific drugs, and refining drug choices based on individualized molecular signatures. This integration of computational tools into personalized medicine ensures that treatment strategies remain adaptive and precisely targeted.

For neurodegenerative diseases like Parkinson's and Alzheimer's, personalized medicine holds significant potential. In Parkinson's disease, targeted interventions can involve combination therapies that modulate multiple inflammatory pathways simultaneously. Real-time biomarker monitoring enables clinicians to adjust treatments according to disease progression, ensuring a continuously optimized approach. Similarly, in Alzheimer's disease, biomarker-driven strategies help identify patients who are most likely to benefit from anti-inflammatory or neuroprotective interventions, improving treatment precision and effectiveness [31].

Despite its promise, personalized medicine faces several challenges. The necessity for extensive molecular profiling demands advanced diagnostic tools and interdisciplinary collaboration among neurologists, immunologists, and bioinformaticians. Additionally, the high cost of genetic testing and precision therapies limits accessibility in many healthcare settings, raising concerns about equitable distribution. Ethical considerations related to data privacy and the integration of AI-driven decision-making further complicate its widespread implementation [32]. Without cost-effective diagnostic frameworks and policies supporting equitable healthcare, personalized medicine may remain inaccessible to many individuals who could benefit from its advancements.

Future progress in this field depends on the development of affordable and scalable diagnostic technologies, AI-integrated treatment models, and broader healthcare policies supporting precision medicine. By incorporating genomic research, machine learning analytics, and real-time biomarker tracking into routine clinical practice, personalized medicine can revolutionize the treatment of neurodegenerative diseases, offering more effective, individualized therapeutic strategies [31].

Conclusion

The review highlights the intricate regulation of microglial and astrocyte activation in neuroinflammation, focusing on key signaling pathways such as NFκB and JAK/STAT. It also underscores the role of metabolic disturbances in driving inflammation and suggests future directions for targeted therapies. While pharmacological agents like NSAIDs, minocycline, and statins offer some therapeutic benefits, their limitations necessitate novel approaches. Advances in computational drug discovery and bioactive compounds, including certain phytochemicals and nootropics, present promising therapeutic avenues. Emerging strategies to enhance drug delivery across the blood-brain barrier, such as nanoparticle-based systems, hold potential for improving treatment efficacy. Additionally, integrating biomarker-driven approaches may facilitate precision medicine strategies, tailoring treatments to individual patient profiles and improving therapeutic outcomes.

Author's contribution

AS (Conceptualization; Investigation; Writing- original draft; Writing- review & editing)
ZK (Data curation; Formal analysis; Methodology; Writing- review & editing)
RN (Supervision; Resources; Validation; Writing- review & editing)
RKD (Project administration; Funding acquisition; Visualization; Supervision)

Conflict of interest

None tp declare.

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