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Neuroinflammation and Potential Therapeutic Strategies: A Narrative Review

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ABSTRACT

Neuroinflammation is a natural and crucial part of the brain's immune response, designed to protect it from pathogens, injuries, and other harmful stimuli. However, when it becomes prolonged or excessive, it can contribute to the development of neurological disorders. It significantly factors into the onset and progression of various neurological disorders, including neurodegenerative diseases, stroke, and traumatic brain injury. It is not just a secondary reaction to injury or infection; rather, it plays a crucial role in the overall pathogenesis of these conditions. This narrative review explores neuroinflammation mechanisms, particularly emphasizing the roles of microglia, astrocytes, and peripheral immune cells. Additionally, some emerging therapeutic strategies have been discussed as potential specific and effective interventions. Despite the substantial advancement, difficulties persist in translating these findings into clinically feasible outcomes. Further investigations focused on mechanistic approaches to inhibit neuroinflammation and its associated disorders are essential for the discovery of novel central nervous system therapies.

Keywords: Microglia; Astrocytes; Peripheral immune cells; Neuroinflammation

INTRODUCTION

Inflammation in the nervous system, also known as neuroinflammation, is a natural immune response within the brain and spinal cord (1). It is a complex process involving various cells and molecules that can have both beneficial and detrimental effects on nervous system function. Neuroinflammation is a crucial pathological driver of several neurological disorders, such as cerebrovascular diseases, traumatic brain and spinal cord injuries, neurodegenerative diseases, epilepsy, multiple sclerosis, psychological disorders, and chronic pain (2). Neuroinflammation is the common mechanism that connects ischemic, degenerative, traumatic, demyelinating, epileptic, and psychiatric pathologies (2). Persistent stress antigens, such as pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and the senescence-associated secretory phenotype (SASP), activate microglia and astrocytes, which in turn trigger inflammatory pathways, including toll-like receptors (TLRs) and nuclear factor kappa B (NF-κB), leading to the release of cytokines like interleukin (IL)-6, tumor necrosis factor-α (TNF-α), IL-1β, and IL-10 (3). These inflammatory mediators can interfere with neurochemical signaling, impairing receptors and other molecular systems essential for neuronal communication (3). Peripheral inflammation, which occurs outside the CNS, triggers a neuroinflammatory response that involves the blood-brain barrier (BBB), glial cells, and neurons (4). Previously thought to completely isolate the CNS from the peripheral immune system, the BBB is now understood to be permeable to pro-inflammatory mediators from peripheral inflammation and can actively release and transmit these mediators. Furthermore, it enables the migration of leukocytes into the brain, contributing to the amplification of neuroinflammatory processes (5).

Neuroinflammatory responses are mediated by several key pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), chemokines (CCL2, CCL5, and CXCL1), secondary messengers (NO and prostaglandins), and reactive oxygen species (ROS) (1). These mediators are released by resident CNS cells, such as microglia and astrocytes, endothelial cells, and peripheral immune cells. Microglia, the resident macrophages of the CNS, are essential players in neuroinflammation. They serve as the first line of immune defense, consistently monitoring the brain environment and reacting to inflammatory stimuli (6). Microglia can be activated in both healthy and pathological conditions, with their activation potentially leading to neuroinflammation that may be either protective or harmful to neuronal health (6). Astrocytes, a type of glial cell, are not merely passive responders in neuroinflammation; they actively participate and play a key role in regulating the inflammatory response in the brain (7). Their involvement can be both beneficial, aiding recovery and tissue repair, and harmful, worsening inflammation and damage. Astrocytes can release both pro- and anti-inflammatory factors, and they interact with various cells in the CNS, including microglia, and respond to signals from these cells (8). These interactions, involving cytokines and surface-to-surface contacts, modulate astrocyte behavior

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and their inflammatory responses (8). Peripheral immune cells, including neutrophils, T lymphocytes, B lymphocytes, and NK cells, significantly contribute to neuroinflammation and may exacerbate neurodegenerative diseases like Alzheimer's and amyotrophic lateral sclerosis (9). These cells can infiltrate the brain, release inflammatory cytokines, and interact with glial cells, ultimately aiding the progression of neuroinflammation and neurodegeneration (10).

Neuroinflammation is driven by multiple molecular pathways, including the NF-κB, NLRP3 inflammasome, Janus kinase–signal transducer and activator of transcription (JAK-STAT), and mitogen-activated protein kinase (MAPK) pathways (11). Following activation by factors such as amyloid beta (Aβ), tau proteins, ROS, and cytokine release, these pathways contribute to the generation of pro-inflammatory cytokines, activation of neurotoxic astrocytes, and the aggravation of oxidative damage (11). Consequently, understanding neuroinflammation and developing targeted therapeutic interventions is crucial for treating and potentially preventing a wide range of neurological and neurodegenerative diseases.

By understanding the mechanisms of neuroinflammation and how it contributes to disease, researchers can develop more effective therapies targeting the underlying inflammation in order to prevent or mitigate its harmful effects. Accordingly, in this study, we review the inflammatory signaling pathways involved in the pathogenicity of major neurodegenerative disorders and also summarize some pharmacological approaches and emerging therapeutic strategies.

METHODOLOGY

For this narrative review, a comprehensive search was conducted across several databases, including PubMed, Science Direct, Google Scholar, and Scopus. The search utilized specific keywords such as “neuroinflammation” and “neurodegenerative disorders,” which were combined with related terms like “Alzheimer’s,” “Parkinson’s,” “Phytochemicals,” “Therapeutic,” “Neurotransmitters,” “Stem cells,” and “Gene Editing.” The review process began with an evaluation of the titles of key references, followed by an assessment of their abstracts. All abstracts of the articles were reviewed to ensure they met the inclusion criteria established for this review. Articles considered unrelated to the review or duplicated in other investigations were excluded. Since this is a narrative review, comprehensive documentation of the literature searches across specific platforms is not required.

Neuroinflammatory Molecular Pathways

Neuroinflammation is triggered by signaling pathways that control the activation of immune cells in the CNS. Firstly, the NF-κB pathway, a key regulator of inflammation (Figure 1), is activated by signals, such as TLRs, TNF-α, and IL-1β, causing the generation of pro-inflammatory cytokines that magnify the inflammatory response (12). Secondly, the JAK-STAT pathway is activated by cytokines such as IL-6 and IL-10, leading to the regulation of immune cell activation, proliferation, and survival (13). In astrocytes, activation of STAT3 has been reported to induce the neurotoxic A1 astrocyte phenotype, thereby increasing neurodegeneration (14).

The NLRP3 inflammasome is reported to have a central role in the innate immune response (Figure 1). The NLRP3 inflammasome, activated by signals such as ROS, triggers the activation of caspase-1, after which pro-inflammatory cytokines IL-1β and IL-18 are released (11). The NLRP3 inflammasome has been associated with neurodegenerative disorders (15). The MAPK signaling pathway, activated during microglial and astrocytic responses (11), has different divisions which include the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. These divisions are activated by different stimuli and facilitate precise cellular outcomes, however, the p38 MAPK pathway is directly activated by IL-1β, TNF-α, and ROS (16). Thereafter, the p38 MAPK pathway induces proinflammatory cytokines and boosts the activity of inflammasomes (11). In microglia, the JNK pathway is activated under stress conditions, which causes a release of neurotoxic factors and apoptosis. Following activation of the p38 MAPK and JNK pathways in astrocytes, cytokines, chemokines, and growth factors are produced. On the other hand, the ERK pathway in astrocytes is not fully understood, however, reports show that it aids astrocytic proliferation and scar formation following CNS injury (11).

Neuroinflammation and Major Neurodegenerative Disorders

The incidence of neurodegenerative diseases has risen in recent years, largely due to increased life expectancy. Alzheimer’s disease (AD) and Parkinson’s disease are among the most prevalent neurodegenerative disorders, characterized by their polygenic, multifactorial, and heterogeneous nature (17, 18). Preventive strategies such as maintaining a healthy diet, regular exercise, and managing comorbidities can help delay their onset. Once diagnosed, therapeutic interventions are essential to slow disease progression (18). In the CNS, heightened inflammatory responses can activate microglial cells, prompting the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These cytokines exacerbate and sustain neuroinflammation, leading to the impairment of healthy neurons and critical brain functions (19).

AD is characterized by a progressive decline in memory, attributed to neurodegeneration driven by the production and accumulation of Aβ peptides in the brain (20). The deposition of Aβ is thought to initiate a cascade of pathological events, including synaptic dysfunction, neuronal damage, and eventual neurodegeneration (20). Inflammatory responses and the release of pro-inflammatory mediators have been implicated in AD, contributing to neuronal loss and cognitive

decline (21). Microglia, the innate immune cells of the CNS, play a critical role in mediating inflammatory responses to pathogens and injury by releasing pro-inflammatory cytokines. Upon activation, microglia secrete cytokines such as TNF-α, which aggravate and propagate inflammation across the brain. These pro-inflammatory factors can further drive neuronal degeneration by activating intracellular signaling pathways, including NF-κB, MAPK, and JNK (11). Cerebrospinal fluid (CSF) biomarkers, including Aβ and tau, are extensively studied in AD and serve as standard indicators of AD pathology. Several investigations have also focused on cytokine levels within the central nervous system of AD patients compared to controls (22).

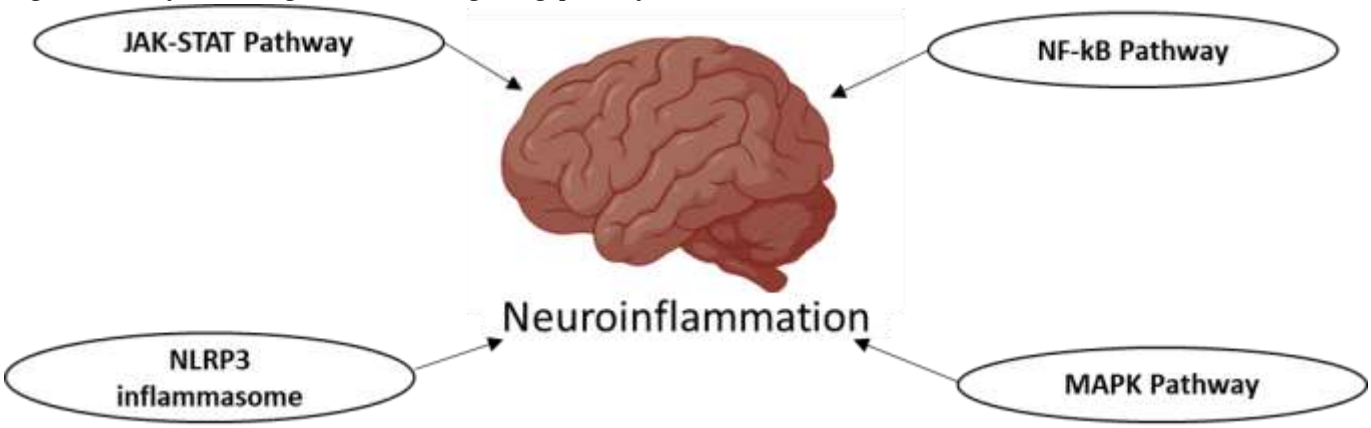


Figure 1. Key Neuroinflammatory molecular pathways.

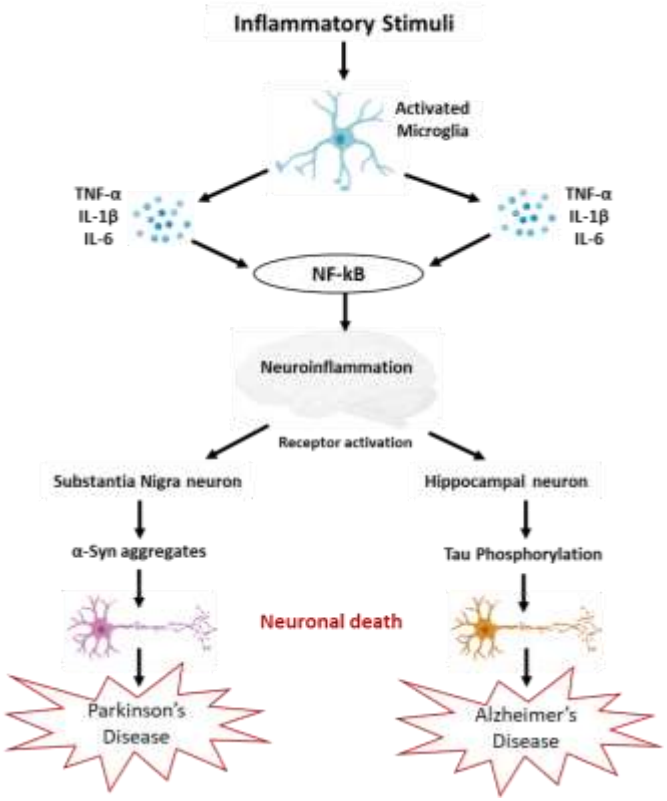


Figure 2: Schematic representation of Neuroinflammation in Alzheimer's and Parkinson's disease sharing a common cascade of molecular signaling due to activation of microglia.

Parkinson's disease (PD) is a chronic and progressive movement disorder characterized by symptoms such as muscular rigidity, tremor, and bradykinesia (17, 23). The underlying cause of PD is the reduction of dopamine, a neurotransmitter critical for motor control, resulting from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. A key pathological hallmark of PD is chronic neuroinflammation; for instance, Glial cell activation, particularly of microglia and astrocytes, is a prominent feature observed in both patients with PD and animal models of the disease (24). In the early stages of neurodegeneration, microglial activation may be beneficial by facilitating the clearance of damaged cells and protecting the CNS. However, excessive or prolonged microglial activation leads to elevated expression of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and IFN-γ (25). These pro-inflammatory mediators contribute to the rapid degeneration of dopaminergic neurons in the substantia nigra pars compacta, thereby exacerbating disease progression.

Furthermore, pro-inflammatory factors released by microglia can activate astrocytes, which further amplify neuroinflammatory processes in PD, perpetuating a vicious cycle of inflammation and neuronal damage (26). Cytokines, chemokines, and other inflammatory mediators are recognized for their role in triggering microglial activation, which may contribute to injury in the nigrostriatal pathway (27, 28). Dopaminergic neurons, which express a broad array of cytokine and chemokine receptors, are believed to be responsive to these inflammatory mediators, whether they originate from or activate microglia. In line with this, elevated expression levels of the chemokine CXCL12 and its receptor CXCR4 have been detected in the substantia nigra highlighting their involvement in neuroinflammatory processes in PD (28). Postmortem studies of the human PD brain and *in-vivo* studies have revealed an upregulation of pro-inflammatory cytokines

such as IL-1β, IL-2, IL-6, IFN-γ, and TNF-α, as well as the anti-inflammatory cytokine IL-10, underscoring the complex inflammatory environment in PD (29, 30).

Potential Therapeutic Interventions

Diverse therapeutic strategies have been developed to address the complex relationship between neuroinflammation, targeting both biochemical and cellular pathways. These strategies can be categorized into pharmacological treatments and emerging therapies. This section reviews the most promising approaches, emphasizing their mechanisms, clinical effectiveness, and associated challenges.

Pharmacological Approaches (2020 – 2025): Anti-Inflammatory Drugs, Phytochemicals, and Medicinal Plants

Current treatments for neuroinflammatory diseases primarily function by inhibiting specific enzymes, antagonizing receptors, or blocking their ligands. Anti-inflammatory drugs, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), are medications that reduce inflammation, pain, and fever. They work by blocking the production of prostaglandins, chemicals in the body that contribute to inflammation and pain. NSAIDs like ibuprofen, aspirin, celecoxib, diclofenac, and naproxen are commonly used. In a recent study examining the effect of aspirin on neuroinflammation in experimental aging mice, results revealed that aspirin treatment resulted in a decreased number of ionized calcium-binding adaptor molecule (Iba)-1 positive microglia, a main cellular element of neuroinflammation in the olfactory bulb when compared to the control group, thus demonstrating the anti-neuroinflammatory properties of aspirin in the olfactory bulb (31). The authors concluded that aspirin can be considered for boosting neural regeneration and management of olfactory deficits in aging and various disorders (31). In a study by Jorda and colleagues, aspirin significantly reduced pro-inflammatory mediators (IL-β and TNF-α) and NF-κB protein expression, inhibited Cyclooxygenase-2 (COX-2) and iNOS, increased anti-inflammatory PPAR-γ protein expression, and ultimately prevented $A\beta_{1-42}$ toxic effects in *in-vitro* astrocyte primary culture (32). This result showed that aspirin attenuates neuroinflammation and prevents the deleterious effects of the $A\beta_{1-42}$ peptide. Shvartsur and coauthors examined the effects of chronic low-dose aspirin and low-dose lithium (Li) treatment on plasma and brain IL-6 and TNF-α production in lipopolysaccharide (LPS)-treated rats (33). The findings showed that the combined treatment attenuated LPS-induced hypothermia and significantly reduced plasma and brain cytokine level elevation, implicating the potential neuroinflammatory inhibiting effects of aspirin (33). Won and coauthors evaluated whether the combined administration of *Gagam-Sipjeondaebo-Tang* herb and ibuprofen affects the inflammatory response of PD in mouse models. Results revealed that co-administration of *Gagam-Sipjeondaebo-Tang* and ibuprofen showed a synergistic effect in improving the loss of dopaminergic neurons and decreasing the activation of macrophages (34). Also, the Nitric oxide level decreased in LPS-stimulated macrophages with this combined treatment. *Gagam-Sipjeondaebo-Tang* herb and ibuprofen administration reduced iNOS, COX-2, IL-1β, and IL-6 levels (34), thus demonstrating a synergistic effect to attenuate neuroinflammation. Alsaegh and colleagues evaluated the anti-inflammatory effect of celecoxib in LPS-pretreated Wistar rats (35). Findings revealed that it decreased the inflammatory effects induced by LPS primarily via the inhibition of COX-2 (35). In a different study, the protective effects of diclofenac on acute inflammation in traumatic spinal cord injury were investigated (36). The authors noted that the inflammatory cells were least in the diclofenac-treated group, thus demonstrating its neuroinflammatory effects. Erdogan and colleagues assessed the impact of diclofenac on seizure and levels of oxidative stress and inflammatory biomarkers in a rat model of epilepsy triggered by pentylenetetrazole (37). Results showed a significant reduction in TNF-α and a lower seizure activity in the rat model of epilepsy, which the authors attributed to the neuroinflammatory inhibiting effects of diclofenac (37).

Efforts to target neuroinflammation using conventional drugs have often been hindered by limited efficacy, adverse side effects, or poor BBB penetration (11). In contrast, phytochemicals with potent antioxidant properties have emerged as a promising alternative. Preclinical studies in animal models have shown encouraging outcomes, and several phytochemicals are now being investigated in clinical trials, either alone or in combination with other therapies, to address neuroinflammation more effectively. Phytochemicals are well-known for their anti-inflammatory effects, both *in-vitro* and *in-vivo*, as demonstrated in various inflammatory disease model systems. By exhibiting mechanisms that reduce chronic inflammation, these compounds hold potential as therapeutic candidates for a range of inflammatory diseases. Their anti-inflammatory action is achieved through the modulation of key signaling pathways, including NF-κB, MAPKs, STAT, and Nrf-2.

Numerous phytochemicals have demonstrated the ability to regulate or suppress neuroinflammation, offering promising therapeutic prospects (38, 39). In a study, the neuroinflammatory effect of rutin, a flavonoid, against the neurotoxin MPP^+ in the human dopaminergic SH-SY5Y cell line was investigated (40). It was observed that rutin significantly reduced protein expression levels of COX-2 in SH-SY5Y cells treated with MPP^+ (40), thus demonstrating its potent neuroinflammatory inhibiting effects. Other flavonoid phytochemical compounds have been reported to inhibit neuroinflammation via their anti-inflammatory and antioxidant properties. For instance, the anti-inflammatory effect of quercetin in the rat primary cortical astrocytes following LPS stimulation was reported (41). Semi-quantitative PCR analysis showed the therapeutic potential of

quercetin by decreasing the gene expression of pro-inflammatory cytokines (IL-1β, IL-6), and COX-2, and increasing Hemeoxygenase-1 in LPS-stimulated astrocytes (41), thus highlighting the anti-inflammatory effects of quercetin against inflammatory responses in astrocytes. Similarly, Lee and colleagues reported that quercetin administration significantly reduced inflammatory markers such as IL-6, IL-1*β*, COX-2, and NF-κB levels in the brain following LPS injection (42). Mayhar and co-workers reported that quercetin significantly increased IL-10 levels and significantly decreased IL-1β levels in the hippocampus of rats following middle cerebral artery occlusion (43). The authors posited that quercetin may help prevent or ameliorate brain injuries caused by acute stroke, suggesting its neuroprotective effects via the reduction in IL-1β and increase in IL-10 as possible mechanisms of action (43). Ahmad and colleagues reported that naringin, a flavanone, significantly reduced the elevated levels of IL-6 and TNF-α in streptozotocin-induced diabetic neuropathy in rat models (44).

Using male APP/PS1 transgenic mice on a C57BL/6 background, Zhu and colleagues reported that naringenin decreased pro-inflammatory cytokine levels in the hippocampus (45). In their study, the results revealed that the mRNA levels of TNF-α and IL-1β were remarkably upregulated in APP/PS1 mice compared with WT mice, while naringenin treatment significantly reduced the expression level of IL-1β mRNA (45). The findings from ELISA also confirmed that naringenin significantly decreased the protein levels of TNF-α and IL-1β in the hippocampus of APP/PS1 mice (46), thus highlighting the anti-inflammatory effect of naringenin. Celikaslan and coworkers investigated the effects of curcumin on neuroinflammation and cognitive function in a rat model of febrile convulsions (47). They reported that curcumin treatment significantly reduced hippocampal TNF-α levels in the febrile convulsion model, thus highlighting its potential as a therapeutic agent in managing febrile seizure-related neuroinflammation (47). The protective effect of nano-curcumin on caffeine-induced neurotoxicity in the cerebrum of rats was investigated by Morsy and colleagues. The findings showed that curcumin caused a significant amelioration in TNF-α and IL-6 levels and a significant downregulation in NF-κB mRNA expression (48), thus demonstrating its anti-inflammatory response in the cerebrum. In a stroke model using mice via middle cerebral artery occlusion, curcumin significantly reduced the number of microglia/macrophages 21 days after stroke (49). Also, the same authors reported that curcumin significantly decreased NLRP3, IL-1*β*, and IL-18 i*n-vitro*, following LPS treatment in primary microglia cells (49). They reported that both *in-vivo* and *in-vitro* studies confirmed that curcumin inhibited the activation of the NF-*κ*B pathway (49), thus highlighting the potent anti-inflammatory activity of curcumin.

Numerous plants are known to inhibit neuroinflammation because they contain substances like polyphenols, terpenoids, and alkaloids that can modulate inflammatory pathways in the brain. Medicinal-plant-based drug discovery remains a key but underexplored area of research with enormous potential. By expansively exploring these plants, researchers can uncover more novel compounds that could offer significant breakthroughs in treating neuroinflammation. In a study, the effect of *Rosmarinus officinalis* on neuroinflammation was investigated by Alrashadi and colleagues using pentylenetetrazol (PTZ)-induced epileptic rats. Findings showed that *Rosmarinus officinalis* significantly decreased TNF-α and IL-6 in the hippocampus of the PTZ-treated rats (50). Similarly, Enogieru and Iyoha reported that *Rosmarinus officinalis* significantly reduced the level of TNF-α in the cerebellum of rats exposed to lead acetate (51), thus demonstrating the anti-inflammatory activity of *Rosmarinus officinalis*. Also, Idemudia and Enogieru reported a significant downregulation of TNF-α in the cerebellum of rats exposed to lead acetate following pretreatment with *Cucumis sativus* (52). Gao and coworkers investigated the protective effect of *Crataegus songarica* against traumatic brain injury (TBI) in rats. The authors reported that *Crataegus songarica* treatment suppressed TBI-induced up-regulation in protein expression levels of IL-6 and TNF-α in the brain cortex (53). Also, treatment of the TBI rats with *Crataegus songarica* suppressed the cortical elevation of NF-κB expression (53).

Alanazi and coworkers investigated the role of Moringa seed extract against Chlorpyrifos-induced cerebral and ocular toxicity in mice. Findings showed that Moringa normalized the pro-inflammatory markers IL-1β, IL-6, and TNF-α in the experimental mice (54). In a different study, *Talinum triangulare* was investigated by Inwang and colleagues for its anti-inflammatory potential in the brain of male Wistar rats. Findings revealed that *Talinum triangulare* significantly reduced TNF-α and IL-6 activities, thus exerting an anti-inflammatory effect in the brains of the experimental rats (55). Zhang and colleagues explored the effects of *Vaccinium arctostaphylos* seed oil on a cerebral ischemic stroke-reperfusion model in Wistar rats and investigated its underlying mechanisms. Findings showed that *Vaccinium arctostaphylos* seed oil treatment progressively increased IL-10 and IL-4 levels and decreased IL-1β, TNF-α, and IL-6, demonstrating *Vaccinium arctostaphylos* 's strong anti-inflammatory properties (56). Khanaki and colleagues evaluated the pretreatment effects of *Lamium album* extract on COX-2 expression in a rat model of middle cerebral artery occlusion. Results revealed that the expression level of COX-2 in the subcortex of the rats exposed to *Lamium album* was significantly decreased relative to the middle cerebral artery occlusion group (57). Akintimehin and coworkers investigated the anti-inflammatory impacts of the methanol extract of *Momordica charantia* leaf in the cortex and hippocampus of cyanide-intoxicated rats. Findings showed that the level of hippocampal TNF-α and IL-6 was significantly decreased following comparison to the cyanide-intoxicated rats (58).

In a different study, Saadullah and colleagues determined the neuroprotective effects of *Cissus tuberosa* against Parkinson's disease by evaluating its impact on neuroinflammation and neurodegeneration in paraquat-induced Parkinson's disease models. Results demonstrated a significant downregulation of IL-6 and TNF-α levels in *Cissus tuberosa*-treated groups, and qRT-PCR results showed significant downregulation of IL-1β and TNF-α mRNA expression in *Cissus tuberosa*-treated groups compared to the diseased group (59). The study concluded that *Cissus tuberosa* has potential therapeutic effects in alleviating PD symptoms, primarily through its anti-inflammatory and neuroprotective properties (59). Oguche and coworkers assessed the anti-inflammatory properties of aqueous leaf extract of *Heinsia crinite* on codeine-induced inflammation in rats. Results revealed decreased TNF-α and IL-6 in the brain of *Heinsia crinite-treated* rats, following comparison to codeine-treated rats (60). In a different study investigating the effect of *Hippophae rhamnoides* on acrylamide-induced brain damage in rats, Turan and coworkers reported that *Hippophae rhamnoides* prevented the increase of IL-1β and TNF-α following acrylamide treatment (61). Huang and coworkers investigated whether *Tiliacora triandra* extract could inhibit Cisplatin-induced redox-mediated neuroinflammation in rats. The authors reported that treatment with *Tiliacora triandra* significantly abated brain levels of TNF-α, IL-6, and IL-1β, thus highlighting the anti-inflammatory effect of *Tiliacora triandra* against Cisplatin (62).

Bukke and colleagues investigated the neuroprotective effect of *Gemlina arborea* stem bark extract in preventing cerebral infarction in Wistar rats. The western blot assay revealed reductions in the inflammatory indicators (p38 MAPK, TNF-α), and significantly raised anti-inflammatory mediators (IL-10 and actin), thus suggesting potential anti-inflammatory mechanisms by which *Gemlina arborea* prevented ischemic reperfusion injury (63). Mostajabi and coworkers investigated the effect of *Cinnamomum zeylanicum* on ischemic tolerance and the expression of matrix metalloproteinase (MMP) 2 and 9 genes, as well as levels of IL-6 and TNF-α proteins in rats receiving a high-fat diet. Findings showed down-regulation of IL-6, TNF-α proteins, and MMP-2,9 levels (64). The authors concluded that *Cinnamomum zeylanicum* may have a neuroprotective effect that may be related to the down-regulation of MMPs and cytokines (64). El Nashar and colleagues investigated the effects of *Stevia rebaudiana* on a PTZ-induced epileptic rat model and its potential mechanisms. Findings showed that *Stevia rebaudiana* significantly downregulated GFAP, IL-6, and NF-κB in the CA3 hippocampal region of experimental rats (65). Spoorthi and coworkers evaluated the antipsychotic activity of ethanolic fruit extract of *Piper longum* and its effect on TNF-α expression in the hippocampus of Wistar rats. The authors reported that *Piper longum* extract significantly reduced the expression of TNF-α in the hippocampus (66).

Furthermore, Auza and colleagues evaluated the effects of *Ginkgo biloba* on mercury chloride-induced neuroinflammation. The result showed a significant decrease in TNF-α and IL-6 activity following comparison to the mercury chloride-treated rats (67). In a different study, Zhang and coworkers explored the protective impact and mechanism of the ethyl acetate extract of *Taxus chinensis* fruits on the hippocampi of rats subjected to chronic unpredictable mild stress. *Taxus chinensis* regulated the excessive activation of hippocampal microglia in rats and inhibited the expression of IL-1β and TNF-α (68). Owemidu and colleagues evaluated the anti-neuroinflammatory properties of the methanol extract of *Waltheria americana* leaf in experimental animals exposed to LPS. Findings showed that the extract significantly decreased IL-6 and TNF-α in the striatum, prefrontal cortex, and hippocampus of rats exposed to LPS (69). ALmohaimeed and coworkers assessed the synergistic effect of *Cinnamomum cassia* and *Zingiber officinale* on neuroinflammation in diabetic rats. Findings revealed that they significantly reduced IL-6, TNF-α, IL1β, as well as hippocampal immunoexpression of GFAP when compared to the untreated diabetic group (70). In a different study, Adebayo and coworkers elucidated the neuroprotective and neurorestorative properties of *Zingiber officinale* methanol extract on nigrostriatal degeneration implicated by immunoinflammatory responses in rotenone-challenged PD mice model. Findings revealed that *Zingiber officinale* significantly attenuated the TNF-α, IL-6 concentrations, COX-2 expression, and MPO activity relative to the untreated rotenone-challenged mice (71), thus demonstrating its potent anti-inflammatory effect.

Emerging Therapies: Stem Cell Therapy, Gene Editing, and Nanotechnology

Given the central role of neuroinflammation in the pathogenesis of various neurodegenerative diseases, novel therapeutic strategies are being actively pursued to mitigate its effects. Among the most promising approaches are stem cell therapy, gene editing, and nanotechnology, each offering distinct potential to address neuroinflammation and its associated complications. These emerging therapies represent a forward-thinking paradigm in the treatment of neurodegenerative disorders, providing new hope for more effective and targeted interventions**.**

Stem Cell Therapy

Stem cells have the unique ability to restore tissue function in two primary ways: they can directly become part of the damaged tissue, functioning as replacement cells, or they can act as carriers to deliver specific signals to the tissue, stimulating its repair mechanisms without actually becoming incorporated into the tissue itself (72). Stem cell therapy holds promise for mitigating neuroinflammation, and literature evidence shows that it occurs in several ways. Firstly, stem cells can directly migrate to the brain and directly secrete anti-inflammatory cytokines and other factors that dampen the

inflammatory response (73). Secondly, stem cells, especially those residing in the spleen, can indirectly modulate the peripheral immune response, which can then impact central neuroinflammation. Thirdly, stem cells can influence the activity of immune cells, such as microglia and astrocytes, to reduce their contribution to neuroinflammation (73). Also, stem cells can promote the regeneration of neurons and other cells in the brain, potentially reducing the overall inflammatory load (73).

Bone marrow-derived stem cells, including mesenchymal stem cells (BM-MSCs), endothelial progenitor cells (EPCs), SB623 cells, multipotent adult progenitor cells (MAPCs), and multilineage-differentiating stress-enduring (Muse) cells, have demonstrated a strong safety profile in various disease indications (74). The potent anti-inflammatory properties of stem cells not only complement the regenerative mechanisms traditionally associated with cell-based therapies, such as cell replacement and the secretion of neurotrophic factors, but also enhance their potential as effective treatments for neurological disorders (75). In preclinical studies, the transplantation of BM-MSCs has demonstrated the potential to mitigate brain injury and enhance both motor and cognitive recovery. Specifically, in a hemorrhagic stroke rat model, intraventricular infusion of BM-MSCs effectively suppressed neuroinflammation by significantly reducing the expression of pro-inflammatory cytokines, including IL-6, IL-1α, and IFN-γ (76). However, with limited evidence supporting the differentiation of MSCs into functional neural cells, an alternative mechanism known as the bystander effect was proposed. This mechanism involves the secretion of growth factors by grafted MSCs, which collectively exert anti-inflammatory, antioxidative, anti-apoptotic, and neurogenic effects; these combined actions are believed to synergistically contribute to more therapeutic outcomes (75). The combined use of BM-MSCs and the peroxisome proliferator-activated receptor gamma (PPARγ) agonist, pioglitazone (PGZ), has demonstrated significant anti-inflammatory effects (77). In PGZ-treated rats, enhanced PPARγ expression facilitated the recruitment of allogeneic BM-MSCs, highlighting the interplay between PPARγ activation and BM-MSCs. Moreover, male stroke models treated with this combined therapy exhibited a marked reduction in IL-6, indicating its potential to counter neuroinflammation (77). Similarly, co-administration of regulatory T cells with BM-MSCs further amplified anti-inflammatory outcomes compared to BM-MSC therapy alone, underscoring the promise of combination therapies in treating neuro-inflammation (77, 78). MSCs therapy holds considerable promise for neuroinflammation treatment, yet it remains in the developmental stage. While a substantial body of preclinical research supports its theoretical feasibility, additional studies are essential to fully elucidate the underlying therapeutic mechanisms and optimize its clinical application.

Gene Editing

Gene therapy has gained attention as a promising therapeutic strategy to modulate the inflammatory response in neurodegenerative diseases. It involves the introduction of a functional gene into cells to correct cellular malfunctions or to provide new capabilities to the cells (79). Innovative genome and transcriptome editing strategies present a remarkable opportunity to uncover novel therapeutic targets, create advanced neurodegenerative disease models, and enhance neuroimaging modalities. These advancements also pave the way for the development of next-generation diagnostics and patient-specific, precision-targeted therapies, which can significantly improve the treatment of neurodegenerative disorders (80). For instance, the genome-editing system CRISPR (clustered regularly interspaced short palindromic repeats) has recently revolutionized biotechnology and biomedical research, offering immense potential in the study of neurodegenerative diseases. CRISPR has been employed to create animal models of PD, including Parkin, DJ-1, and PINK1 triple knockout miniature pigs (81). This innovative technology has enabled a deeper understanding of gene interactions in PD and has facilitated the identification of novel apoptotic pathways involved in neurodegeneration, thereby advancing therapeutic strategies for neurodegenerative disorders.

In AD, CRISPR-Cas9 technology has also demonstrated remarkable precision and efficiency in correcting genetic mutations, particularly in genes associated with AD, such as APP, PSEN1, and PSEN2 (82). This innovative tool has opened new avenues for the development of novel AD models, significantly enhancing both diagnostic and therapeutic approaches. By enabling targeted genetic modifications, CRISPR-Cas9 advances understanding of the nervous system, allowing for more comprehensive studies from *in-vitro* cellular models to *in-vivo* animal models, and offering hope for more effective treatments for AD (83). Although gene editing holds significant promise for treating neurodegenerative diseases, several challenges remain. These include off-target effects, the complexity of delivery mechanisms, and ethical concerns surrounding germline editing, all of which need to be addressed before the widespread clinical application of these technologies.

Nanotechnology

Nanotechnology, the design and manufacture of systems or devices at the molecular scale, is a rapidly advancing multidisciplinary field with transformative potential. Nanotechnology's origins are rooted in a vision of transformative advancements in medicine, communications, and genomics, aiming to reshape these fields fundamentally (84). This vision focuses on using nanoscale materials and processes to address complex challenges, particularly in targeted drug delivery, advanced diagnostics, and personalized medicine. The promise of nanotechnology lies in its potential to revolutionize healthcare, improve communication

technologies, and advance our understanding of genetic information (84).

Nanoparticles, particularly those made from liposomes, dendrimers, micelles, and carbon nanotubes, can be engineered to cross the BBB and deliver targeted therapies directly to affected areas in the brain (85). These nanoparticles can encapsulate anti-inflammatory drugs, cytokine inhibitors, or gene-editing tools, offering a highly localized treatment approach. Nano-drug delivery systems can enhance anti-inflammatory nanomedicines by addressing unfavorable physicochemical properties, extending systemic circulation time, and minimizing off-target drug toxicity (86). In recent decades, significant efforts have been directed toward developing Nano-drug delivery systems capable of synchronously co-delivering multiple therapeutic agents and/or diagnostic probes against inflammatory diseases (87). Several studies have demonstrated the use of nanotechnology to reduce microglial activation (88), inhibit the release of inflammatory cytokines (89), and prevent neurodegeneration in experimental models (46). However, challenges such as biocompatibility, long-term safety, and controlled drug release need to be addressed before these therapies can be applied clinically.

Conclusion: The intricate relationship between inflammation and the nervous system profoundly influences the progression of a range of neurological disorders. As research unravels the complex mechanisms involved, it becomes increasingly clear that targeting neuroinflammatory pathways presents a promising therapeutic intervention avenue. Various strategies, including pharmacological treatments, hold the potential for mitigating neuroinflammation in the CNS. Future studies focusing on the development of personalized approaches that consider individual variability in neuroimmune responses are strongly recommended. Moreover, integrating emerging technologies, such as nanotechnology, stem cell therapy, and phytochemicals as drug supplements, may enhance the efficacy of anti-inflammatory treatments while minimizing side effects.

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