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Medicinal Plants and Bioactive Phytochemicals Targeting Neuroinflammation: Molecular Mechanisms, Preclinical Evidence and Translational Challenges

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Abstract

Neuroinflammation is the inflammatory response within the central nervous system which is linked to many neurological disoders. These disorders include Alzheimer's disease, Parkinson's disease, multiple sclerosis, ischemic stroke, among others. Short-term reaction to inflammation within the central nervous system has a contribution to the balance of neural homeostasis and protection of tissues but once the neuroinflammation is persistent, it may lead to the production of inflammatory mediators in excess, oxidative stress, and gradual neuronal damage. Increasing evidence suggests that persistent triggering of microglia and astrocytes, and also the disruption of signaling cascades like nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and NLRP3 inflammasome pathways, plays major role in the progression of neurodegenerative diseases. A lot of attention has been given to medicinal plants as a therapeutic agent that has prospects due to their wide range of phytochemicals and multi-target pharmacological effects. Many plant-based compounds such as curcumin, epigallocatechin-3-gallate, ginsenosides, withanolides, and bacosides have shown properties of anti-neuroinflammation and neuroprotection by inhibiting inflammatory signaling pathways, reducing microglial activation, reduction of oxidative stress, and increasing support for neuron survival. This review gives an in-depth review of medicinal plants with anti-neuroinflammatory properties, focusing on their bioactive compounds, mode of action, and clinical applications in neurological disorders. The current challenges, limitations and future research viewpoint relating to the clinical application of medicinal plant compounds are discussed. The findings show that medicinal plants are potential treatment options for neuroinflammatory disorders.

Introduction

Neuroinflammation represents a biological process that plays a role in the development and progression of several neurological disorders. Under physiological conditions in the central nervous systems, inflammatory responses play a vital role in how a tissue maintains balance, removal of pathogens and enhancing tissue repair after injury (Yao et al., 2020). A dysfunction in how a neuron functions and gradual death of the nerve cell may be as a result of the damaging effects of chronic inflammatory response. The important glial cells that sustain the immune environment of the CNS are the microglia and astrocytes. The microglia which is the brain's key immune cell monitors the brain's environment, protect neurons and causes synaptic plasticity (Cherry et al., 2014). The microglia are being activated when pathological conditions such as infection, traumatic injury, aging, environmental stressors or exposure to toxic substances is detected. Once detected, inflammatory signaling cascades is being initiated (Yao et al., 2020). It was also noted that if microglial activation is being sustained it may interfere with the normal regulation that goes on within the neural tissues.

Excessive production of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), nitric oxide (NO), prostaglandins, and reactive oxygen species (ROS) are linked to the sustained activity of the microglia. These inflammatory mediators contribute greatly to increasing inflammation within the CNS (Glass et al., 2010). It was also observed that chronic exposure to inflammatory molecules may amplify oxidative damage and facilitate neuronal injury.

Evidence has shown the link between chronic neuroinflammation and the pathogenesis of various neurodegenerative and neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, traumatic brain injury, and ischemic stroke (Barbalho et al., 2025). Persistent inflammatory response has been shown to have a direct connection with the buildup of amyloid-β and tau hyperphosphorylation in Alzhemer's disease (Heneka et al., 2015). In Parkinson's disease, inflammatory mediators contribute to the degeneration of dopaminergic neurons found within the substantia nigra. A cycle that constantly leads to the progression of disease and loss of neurons is caused as a result oxidative stress and inflammatory signaling pathways triggering each other.

A wide range of molecular pathways have had involvement in the regulation of neuroinflammatory responses such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), toll-like receptor (TLR), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and NLRP3 inflammasome pathways, and has gained a lot of research attention because of the role they play in neuronal degeneration and inflammatory amplification (Kaur and Chugh, 2020). A dysregulation of these pathways could lead to an increase in the production of inflammatory mediators, mitochondrial dysfunction, cellular stress, and programmed cell death, which would facilitate the progression of disease (Heneka et al., 2015).

Recently, the therapeutic approach to neurodegenerative diseases primarily looks at how symptoms are managed and hampering disease progression but conventional therapies always show limitations such as adverse effects, poor long-term efficacy, blood-brain barrier penetration restriction, and insufficient targeting of several disease pathways. Despite these setbacks, a good number of attention has shifted to finding more safer and effective treatment options.

History shows that medicinal plants are important sources of active biological compounds and continue to contribute immensely to modern drug discovery. Compounds derived from plants such as flavonoids, alkaloids, terpenoids, polyphenols, and phenolic acids possess tremendous antioxidant, anti-inflammatory, and neuroprotective activities (Khan et al., 2021). Based on evidence from experiments, it is shown that the phytochemical constituents of medicinal plants can attenuate neuroinflammatory responses by suppressing microglial activation, pro-inflammatory cytokine

release reduction, inhibition of oxidative stress, and the modulation of intracellular inflammatory signaling pathways (Liu et al., 2018). Curcumin, epigallocatechin gallate, quercetin, ginsenosides, and withanolides, which are bioactive molecules have shown anti-neuroinflammatory and neuroprotective effects, which are promising in both in vitro and in vivo studies.

A detailed and comprehensive review of medicinal plants is needed because of an increase in neurodegenerative diseases and the shortcomings of recent therapeutic approaches. This review aims at reviewing medicinal plants that has anti-neuroinflammatory properties by focusing on their bioactive constituents, mechanism of actions, and its therapeutic applications in neurological disorders. Current challenges and future perspectives regarding the advancement of plant-derived compounds into clinical trials and therapeutic applications are also discussed.

Pathophysiology of Neuroinflammation

Neuroinflammation is a complex and highly regulated immune response within the central nervous system (CNS) that occurs after exposure to harmful stimuli such as infections, traumatic injury, ischemia, toxic agents, protein aggregation, and neurodegenerative processes (Glass et al., 2010; Heneka et al., 2015). Under normal physiological conditions, inflammatory responses help give protection by helping in the maintenance of neuronal balance, tissue repair facilitation, and removal of harmful agents although imbalances in inflammatory activities may become dangerous and have a significant contribution to the progression of neuronal damage and disease development (Yao et al., 2020). The microglia and astrocytes are the primary cellular mediators involved in neuroinflammatory processes. Microglia function as resident macrophage-like immune cells within the CNS and constantly search the body for abnormal cells and pathogens and removes them before they lead to disease progression (Cherry et al., 2014). Microglia contribute greatly to neuronal maintenance by regulating how the brain modify, strengthen weaken, form or eliminate the synapses that are between neurons in response to activity, experience, development or injury, and removing cellular debris under physiological conditions (Colonna and Butovsky, 2017). Other pathological stimuli that can trigger chronic activation of the microglia are aging, oxidative stress, infections, and accumulation of toxic proteins, and can lead to changes in the morphology and function of the cell.

The activation of microglia releases a wide range of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), nitric oxide (NO), prostaglandins, chemokines, and reactive oxygen species (ROS). The release of these mediators in excess may affect the pathways of neuronal signaling and hastens neuronal degeneration (Liu et al., 2018). It was suggested that chronic exposure to these mediators enhances oxidative stress and contribute to neuronal dysfunction (Yao et al., 2020).

Astrocytes also play very important roles in neuroinflammatory responses. Under normal conditions, astrocytes help in the maintenance extracellular ion balance, regulation of neurotransmitter homeostasis, and provide metabolic support for neurons, but reactive astrocytes may go through functional changes and contribute to inflammatory amplification by releasing pro-inflammatory cytokines and chemokines. Astrocytes activation can induce neurotoxic responses that have the capability to enhance neuronal injury and disease progression (Liddelow et al., 2017).

In the regulation of neuroinflammation several intracellular signaling pathways have been affected and one of them is the nuclear factor-kappa B (NF-κB) signaling pathway which is one of the most studied inflammatory pathways because of its regulatory effects on genes that are associated with immune activation and production of inflammatory mediators. Activation of NF-κB shows how the inflammatory molecules such as TNF-α, IL-1β, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) are expressed, thereby promoting inflammatory responses (Lawrence 2009).

Mitogen-activated protein kinase (MAPK) signaling pathways, which include extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 pathways, also have great contributions to inflammatory signal transduction. It was observed that a dysregulation in the MAPK signaling is linked with inflammatory progression and neuronal dysfunction (Kim and Choi, 2010). Abnormal MAPK activation may give rise to the development of neurodegenerative disorders (Yao et al., 2020).

Activation of the NLRP3 inflammasome complex is another important mechanism that has an association with the progression of neuroinflammation. The activation of NLRP3 promotes the maturation and release of inflammatory cytokines such as IL-1β and IL-18, which help maintain inflammatory signaling (Heneka et al., 2013). Excessive NLRP3 activation is associated with several neurodegenerative disorders, including Alzheimer's disease and multiple sclerosis (Voet et al., 2019).

Through oxidative stress, neuroinflammatory pathology occurs by the excessive production of reactive oxygen species and mitochondrial dysfunction. Increased ROS generation can cause damage to proteins, lipids, and nucleic acids, thereby having an adverse effect on normal cellular function (Angelova and Abramov, 2018). Oxidative stress and inflammatory signaling frequently interact through reciprocal mechanisms, thereby resulting in a self-amplifying cycle that enhances neuronal degeneration.

Medicinal Plants and their Anti-neuroinflammatory Activities

Medicinal plants have a wide range of phytochemical constituents and because of this it has drawn a lot of interest. Numerous studies have shown that the bioactive compounds derived from plants has anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects which is very useful in neuroinflammatory disorders management. Phytochemicals can exert their neuroprotective effects by modulating inflammatory signaling pathways, reducing oxidative stress, and regulating immune responses.

Polyphenol-Rich Medicinal Plants: *Curcuma longa and Camellia sinensis*

Polyphenol-rich medicinal plants got a lot of attention because of their ability to reduce neuroinflammation through different mechanisms. Among these plants, *Curcuma longa* (turmeric) and *Camellia sinensis* (green tea) are the most widely studied. Their major bioactive compounds are curcumin and epigallocatechin-3-gallate (EGCG) and they have shown potent antioxidant, anti-inflammatory, and neuroprotective effects in several experimental studies (Heneka et al., 2015; Hewlings & Kalman, 2017; Khan et al., 2021).

Curcumin, the main active compound in *Curcuma longa*, has shown the capability to reduce the activation of microglia and astrocytes which are the major immune cells involved in neuroinflammation. It also reduces the production of inflammatory mediators (Kaur & Chugh, 2020; Yao et al., 2020). In Alzheimer's disease, Parkinson's disease, and cerebral ischemia, the animal models showed that curcumin reduced oxidative stress, improved cognition and prevented neuronal degeneration (Wang et al., 2021; Shen et al., 2024).

Camellia sinensis which is rich in catechins, especially EGCG, has demonstrated important anti-neuroinflammatory effects. Epigallocatechin-3-gallate reduces microglial activation, suppresses inflammatory cytokines, and protects neurons against oxidative damage (Mandel et al., 2011; Liu et al., 2018). It also aids in the regulation of inflammatory pathways thereby helping to reduce neuronal injury and improve the brain's function in experimental models (Khan et al., 2021; Shen et al., 2024).

Although curcumin and EGCG are chemically different, they share many similar actions. They both cause oxidative stress reduction, inflammatory signaling suppression, and limitation of the release of pro-inflammatory cytokines, which helps protect neurons from damage caused by inflammation (Cherry et al., 2014; Heppner et al., 2015). Their clinical use still has shortcomings because both compounds have low bioavailability and are metabolized rapidly

after administration (Anand et al., 2007; Hewlings & Kalman, 2017).

Figure 1: *Curcuma longa*

Figure 2: *Camellia sinensis*

Adaptogenic Medicinal Plants: *Withania somnifera and Bacopa monnieri*

Adaptogenic medicinal plants are known for their ability to protect the body against physical and biological stress. The most widely studied are the *Withania somnifera* (Ashwagandha) and *Bacopa monnieri* (Brahmi). They are studied for their neuroprotective and anti-neuroinflammatory effects. These plants contain different bioactive compounds but produce effects that are similar by reducing inflammation, oxidative stress, and neuronal damage (Kaur & Chugh, 2020; Khan et al., 2021).

The main active compounds in *Withania somnifera* are withanolides, which possess antioxidant and anti-inflammatory properties. Studies have shown that withanolides reduce microglia and astrocytes activation and lower the production of inflammatory cytokines (Yao et al., 2020; Shen et al., 2024). These compounds regulate inflammatory pathways, including NF-κB, by helping to reduce neuronal damage and improve brain function in experimental models of Alzheimer's and Parkinson's diseases (Kaur & Chugh, 2020; Wang et al., 2021).

Bacopa monnieri contains triterpenoid saponins known as bacosides, which are mainly responsible for its pharmacological effects. It have been reported that bacosides has the ability to reduce oxidative stress, suppress inflammatory mediators, and enhance the activity of antioxidant enzymes such as superoxide dismutase and catalase (Liu et al., 2018; Khan et al., 2021). *Bacopa monnieri* improves learning, memory, and synaptic function, and this makes it one of the most widely studied medicinal plants for cognitive disorders (Aguiar & Borowski, 2013; Shen et al., 2024).

Although *Withania somnifera* and *Bacopa monnieri* contain different phytochemicals, they both help in reducing neuroinflammation by suppressing the activation of glial, reducing oxidative stress, and protecting neurons from the danger of inflammatory damage (Cherry et al., 2014; Heppner et al., 2015). Ashwagandha is widely recognized for its anti-inflammatory and adaptogenic effects and Brahmi has shown greater benefits in improving memory and cognitive performance.

Figure 3: *Withania somnifera*

Figure 4: *Bacopa monnieri*

Immunomodulatory Medicinal Plants: *Panax ginseng, Zingiber officinale, and Waltheria americana*

Medicinal plants with immunomodulatory properties help regulate immune responses and reduce excessive inflammation in the central nervous system. Among all the immunomodulatory medicinal plants, the most studied are *Panax ginseng* (ginseng) and *Zingiber officinale* (ginger). In recent times *Waltheria americana* has gained attention because it has anti-inflammatory and analgesic properties, which suggests that it may have potential in neuroinflammatory disorders management.

The therapeutic effects of *Panax ginseng* are mainly due to ginsenosides. This ginsenosides have shown the ability to reduce microglial activation and decrease the production of inflammatory cytokines (Kim et al., 2018; Kaur & Chugh, 2020). Ginsenosides also reduce oxidative stress and improve survival of neurons by regulating inflammatory signaling pathways (Liu et al., 2020; Shen et al., 2024). In Alzheimer's disease and Parkinson's disease, the experimental models showed that treatment with ginseng significantly improved memory, reduced neuronal loss, and decreased neuroinflammation (Ratan et al., 2021).

Zingiber officinale has also shown neuroprotective effects that are promising. Gingerols and shogaols are its major bioactive compounds and they possess very potent antioxidant and anti-inflammatory properties (Mashhadi et al., 2013). Experimental studies have shown that ginger reduces oxidative stress, suppresses inflammatory cytokines, and prevent neurodegeneration caused by chronic inflammation (Semwal et al., 2015; Khan et al., 2021). These findings suggest that ginger may help slow the progression of neurodegenerative diseases.

Waltheria americana is a medicinal plant with anti-neuroinflammatory potential. In an LPS-induced neuroinflammation model, the methanol leaf extract significantly reduced the pro-inflammatory cytokines IL-6 and TNF-α in the hippocampus, prefrontal cortex, and striatum, and preserved dendritic arborization. This shows that there is a protection against neuroinflammatory damage (Owemidu et al., 2022). The major constituents of the extract as identified by gas chromatography-mass spectrometry (GC-MS) analysis are fatty acids and methyl esters, and they may contribute to its observed neuroprotective effects (Owemidu et al., 2022).

Panax ginseng, Zingiber officinale, and *Waltheria americana* represent medicinal plants with significant anti-inflammatory potential. The neuroprotective effects of ginseng and ginger are widely supported by lots of experimental evidence, but research on *Waltheria americana* is still in its early stages.

Figure 5: *Panax ginseng*

Figure 6 *Zingiber officinale*

Figure 7: *Waltheria americana*

Medicinal plants have diverse phytochemical constituents that have the ability and are capable of targeting multiple mechanisms that are involved in neuroinflammation. Their ability to regulate inflammatory mediators, reduce oxidative stress, suppress microglial activation, and protect neurons suggests a great amount of therapeutic potential in neuroinflammatory and neurodegenerative disorders.

Mechanisms of Action of Medicinal Plants in Neuroinflammation

Multiple interconnected mechanisms such as modulation of inflammatory signaling pathways, regulation of oxidative stress, suppression of immune cell activation, and protection against neuronal injury are the ways by which medicinal plants exert their anti-neuroinflammatory effects. Conventional therapeutic agents often target single molecular pathways, while plant-derived bioactive compounds possess multitarget activities that may simultaneously influence various biological processes implicated in neuroinflammation. These broad pharmacological effects have gained significant interest in medicinal plants as potential therapeutic agents for neurodegenerative disorders.

Modulation of Microglial and Astrocyte Activation

The major immune cells of the central nervous system are the microglia and astrocytes and they play an important role in maintaining brain homeostasis. These cells support neuronal function, clear cellular debris, and help maintain synaptic activity under normal conditions. But during infection, brain injury, or neurodegenerative diseases, they become overactivated and release large amounts of pro-inflammatory cytokines, chemokines, nitric oxide, and reactive oxygen species which leads to chronic neuroinflammation and neuronal damage (Cherry et al., 2014; Heneka et al., 2015).

Regulating the activation of microglia and astrocytes instead of suppressing their normal functions completely is a way by which many medicinal plants reduce neuroinflammation. Phytochemicals such as curcumin from Curcuma longa, epigallocatechin-3-gallate (EGCG) from *Camellia sinensis*, withanolides from *Withania somnifera*, bacosides from *Bacopa monnieri,* ginsenosides from *Panax ginseng*, and gingerols from *Zingiber officinale* as shown by experimental evidences reduces excessive glial activation and limit the release of inflammatory mediators (Kaur & Chugh, 2020; Barbalho et al., 2025).

Once glial activation is reduced the phytochemicals decrease the production of inflammatory cytokines, while also lowering oxidative stress within the brain. This helps in the preservation neuronal structure, improve synaptic function, and reduce the progression of neurodegenerative disorders. As suggested by further studies, these compounds aids in a shift from the microglia pro-inflammatory phenotype towards a state of protection and tissue repair. This helps in the resolution of inflammation rather than simply blocking it (Zhao et al., 2025; Barbalho et al., 2025).

Regulation of Pro-inflammatory Cytokines and Chemokines

A major feature of neuroinflammation is the excessive production of pro-inflammatory cytokines and chemokines. Once microglia and astrocytes are being activated, inflammatory mediators are released. Although host defense and tissue repair are the important roles these molecules play, the constant production contributes greatly to neuronal injury, synaptic dysfunction, and neurodegenerative diseases progression (Glass et al., 2010; Heneka et al., 2015).

Table 1: Medicinal Plants with Reported Anti-Inflammatory Activities and Their Mechanisms of Action

Medicinal Plant	Major Bioactive Constituent(s)	Mechanism of Anti-Neuroinflammatory Action	Experimental Model	Key Findings	References
Curcuma longa (Turmeric)	Curcumin	Curcumin suppresses NF-kB activation which then reduces the production of pro-inflammatory cytokines and limiting oxidative stress	In vitro and animal studies	Reduced microglial activation and decreased neuroinflammatory responses	Hewlings and Kalman (2017); Amalraj et al., 2017
Waltheria americana	Fatty acids, methyl esters	Reduced the expression pro-inflammatory cytokines (IL-6 and TNF-α), attenuated neuroinflammation, and preserved neuronal integrity	Animal studies	Reduction in IL-6 and TNF-α concentration in the hippocampus, prefrontal cortex, and striatum, and intact dendritic architecture	Owemidu et al., 2022
Camellia sinensis (Green Tea)	Epigallocatechin-3-gallate EGCG), catechins	Exert potent antioxidant effects by scavenging ROS, and inhibiting inflammatory signaling pathways	Cell culture and animal studies	Improved neuronal survival, reduced oxidative damage and neuroinflammatory responses	Weinreb et al., 2004; Mandel et al., 2008
Withania somnifera (Ashwagandha)	Withanolides	Suppression of inflammatory cytokines, antioxidant activity, neural protection	Animal studies	Reduced inflammation together with improvements in cognitive functions	Kuboyama et al., 2006; Dar et al., 2015
Bacopa monnieri	Bacosides	Alleviates oxidative stress and regulate inflammatory signaling pathways, thereby promoting neuroprotection	Experimental studies	Improved neuronal function and attenuated inflammatory damage	Kongkeaw et al., 2014
Panax ginseng	Ginsenosides	Inhibition of microglial activation and suppress the release inflammatory cytokine production.	In vitro and in vivo studies	Reduced neuroinflammatory markers and enhanced neuronal survival following treatment with ginsenosides	Ratan et al., 2021
Zingiber officinale (Ginger)	Gingerols, shogaols	Suppression of inflammatory mediators and oxidative stress	Experimental studies	Reduced inflammatory responses and neuronal damage	Mashhadi et al., 2013

Ginkgo biloba	Flavonoids, terpenoids	Exert antioxidant effects and modulate inflammatory signaling pathways thereby limiting neuro-inflammatory response	Animal and clinical studies	Improved cognitive performance and reduced neuroinflammation	Ahlemeyer and Krieglstein 2003
Rosmarinus officinals (Rosemary)	Rosmarinic acid, carnosic acid	Reduction of oxidative stress and inhibition of inflammatory signaling pathways	Experimental studies	Neuroprotective activity against inflammatory-induced neuronal injury	Habtemariam 2006
Centella asiatica	Asiaticoside, Asiatic acid	Regulate cytokine production and enhances antioxidant defense	Animal studies	Reduced neurotoxicity and inflammation while promoting neuronal protection	Gray et al., 2018
Glycyrrhiza glabra (Licorice)	Glycyrrhizin, flavonoids	Suppression of inflammatory mediators and reduction of oxidative stress	Experimental studies	Decreased neuroinflammatory responses following treatment with *Glycyrrhiza glabra*	Postorino et al., 2018

Table 2: Major Molecular Pathways Targeted by Medicinal Plant-Derived Compounds in Neuroinflammation

Bioactive Compound	Plant Source	Molecular Target/Pathway	Biological Effect	References
Curcumin	*Curcuma longa*	NF-kB, MAPK	Reduction in cytokine production and oxidative stress	Hewlings and Kalman 2017
Fatty acids, methyl esters	*Waltheria americana*	Reduced IL-6 and TNF-α production	Reduced neuroinflammation, preserved dendritic architecture, and improved spatial memory	Owemidu et al., 2022
EGCG	*Camellia sinensis*	ROS signalling pathways, NF-kB	Antioxidant and anti-inflammatory effects	Mandel et al., 2008
Ginsenosides	*Panax ginseng*	NF-kB, MAPK	Inhibition of microglial activation	Ratan et al., 2021
Withanolides	*Withania somnifera*	Cytokine signalling pathways	Reduced inflammatory responses	Dar et al., 2015
Bacosides	*Bacopa monnieri*	Oxidative stress pathways	Neuroprotection and reduced cellular damage	Kongkeaw et al., 2014
Gingerols	*Zingiber officinale*	NF-kB and oxidative stress pathways	Reduced inflammatory mediator production	Mashhadi et al., 2013
Rosmarinic acid	*Rosmarinus officinalis*	MAPK and ROS pathways	Reduced oxidative stress and neuronal injury	Habtemariam 2016
Glycyrrhizin	*Glycyrrhiza glabra*	HMGB1 inflammatory pathway	Suppression of neuroinflammation	Postorino et al., 2018

Many medicinal plants exert their anti-neuroinflammatory effects by reducing the production of these inflammatory mediators. Curcumin from *Curcuma longa* decreases the expression of TNF-α, IL-1β, IL-6, COX-2, and iNOS, thereby limiting inflammatory responses in the brain (Hewlings & Kalman, 2017; Kaur & Chugh, 2020). Epigallocatechin-3-gallate (EGCG), the major catechin in *Camellia sinensis*, inhibits the release of inflammatory cytokines and causes nitric oxide production reduction in activated microglia (Mandel et al., 2011; Khan et al., 2021).

Withania somnifera, *Bacopa monnieri, Panax ginseng, and Zingiber officinale* have similar effects. Their major phytochemicals reduce inflammatory cytokine production while improving antioxidant defenses which results in lower oxidative damage and better neuronal survival (Aguiar & Borowski, 2013; Kim et al., 2018; Semwal et al., 2015).

Recent experimental evidence also supports the anti-neuroinflammatory potential of *Waltheria americana.* By using an LPS-induced neuroinflammation model, the methanol leaf extract significantly reduced the concentrations of IL-6 and TNF-α in the hippocampus, prefrontal cortex, and striatum, improved spatial memory, and preserve neuronal morphology (Owemidu et al., 2022). These findings shows that *Waltheria americana* exerts its neuroprotective effects through the suppression of pro-inflammatory cytokine production and reduce neuroinflammatory responses.

Modulation of Inflammatory Signaling Pathways

Inflammatory signaling pathways play a major role in the development and progression of neuroinflammation. The production of pro-inflammatory cytokines, chemokines, and other inflammatory mediators that has a role in neuronal damage is being stimulated once it is triggered by infection, injury, or toxic substances. Nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome are among the most important pathways (Heneka et al., 2015; Ransohoff, 2016).

The NF-κB signaling pathway is one of the main regulators of neuroinflammation. Once this NF-κB pathway is activated, there will be an increase in the expression of inflammatory mediators which thereby support inflammatory responses in the brain (Glass et al., 2010; Cherry et al., 2014). Many plant-derived phytochemicals have been reported to inhibit NF-κB activation, which then result in the reduction of cytokine production and neuronal survival improvement (Kaur & Chugh, 2020; Barbalho et al., 2025).

The MAPK pathway, which includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, also plays an important role in regulating inflammatory responses. If these kinases are activated excessively there would be increase microglial activation and release of inflammatory cytokines.

Excessive activation of these kinases promotes microglial activation and increases the release of inflammatory cytokines. Experimental studies have shown that several medicinal plant constituents extenuate MAPK signaling, which then reduces inflammation and limits neuronal injury (Yao et al., 2020; Shen et al., 2024).

The JAK/STAT signaling pathway is another important pathway, which controls immune and inflammatory responses in the central nervous system. Chronic activation of this pathway is associated with chronic neuroinflammation and neurodegeneration. Recently, evidence suggests that several plant-derived compounds can help modulate JAK/STAT signaling, which will then in turn lead to a reduction in inflammatory responses and improved neuronal protection (Leng & Edison, 2021; Barbalho et al., 2025).

The NLRP3 inflammasome is a major therapeutic target in neuroinflammation. NLRP3 complex activation promotes the maturation and release of IL-1β and IL-18, which amplify inflammatory responses and contribute to neuronal damage. As stated by a growing number of studies, medicinal plant phytochemicals can inhibit NLRP3 activation. As a result of the inhibition, there will be a

reduction in inflammasome-mediated inflammation and slow progression of neurodegenerative diseases (Heneka et al., 2015; Swanson et al., 2019; Shen et al., 2024).

Oxidative Stress Reduction and Antioxidant Defense Enhancement

Oxidative stress is a major factor in the development of neuroinflammation and neurodegenerative diseases. It occurs when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and exceeds the ability of the body's antioxidant defense system. Once oxidative stress is in excess it damages lipids, proteins, DNA, mitochondria, and leads to neuronal dysfunction and cell death (Barnham et al., 2004; Cobley et al., 2018). Oxidative stress and neuroinflammation come together and creates a cycle that increases disease progression (Heneka et al., 2015).

Strengthening the brain's antioxidant defense system is one of the ways many medicinal plants reduce neuroinflammation. The medicinal plant's bioactive compounds collect and remove free radicals, reduce lipid peroxidation, and increase the activity of antioxidant enzymes (Khan et al., 2021; Barbalho et al., 2025). The end result is neuronal cells becoming more resistant to oxidative injury and inflammatory damage.

In experimental models of neurological diseases, Curcumin from *Curcuma longa*, EGCG from *Camellia sinensis*, withanolides from *Withania somnifera,* bacosides from *Bacopa monnieri*, ginsenosides from *Panax ginseng*, and gingerols from *Zingiber officinale* have all been reported to reduce oxidative stress. These phytochemicals improve the capacity of antioxidants, preserve mitochondrial function, and reduce the accumulation of reactive oxygen species (Hewlings & Kalman, 2017; Kim et al., 2018; Shen et al., 2024).

In *Waltheria americana,* the precise antioxidant mechanisms require more investigation. Owemidu et al., (2022) demonstrated that the methanol leaf extract protected neuronal architecture and prevented LPS-induced neurotoxicity in experimental animals. Based on these findings, it suggests that *Waltheria americana* anti-neuroinflammatory activity may be associated with reduced oxidative damage and preservation on neuronal integrity.

Protection against Neuronal Apoptosis

An important feature of many neurodegenerative diseases is neuronal apoptosis. Chronic neuroinflammation and oxidative stress damages the mitochondria, which leads to a reduction in ATP production, increased reactive oxygen species (ROS) generation, and activation of apoptotic pathways. As neuronal loss increases, there is a gradual decline in cognitive and motor functions (Mattson, 2007; Wang et al., 2023).

Several medicinal plants protect neurons by preserving the function of the mitochondria and reducing apoptosis. Experimental evidence shows that phytochemicals help in the maintenance of mitochondrial integrity, energy metabolism improvement, and oxidative damage reduction (Khan et al., 2021; Shen et al., 2024). The bioactive compounds help in regulating apoptosis-related proteins by causing the increment of anti-apoptotic proteins expression such as Bcl-2 while reducing the expression of pro-apoptotic proteins, including Bax and caspase-3, thereby promoting neuronal survival (Elmore, 2007; Barbalho et al., 2025). The neuroprotective effects of *Waltheria americana* recently demonstrated in an experimental model of LPS-induced neuroinflammation. The methanol leaf extract treatment caused an intact dendritic architecture and improved behavioral performance, which indicated that there was protection against inflammation-induced neuronal injury (Owemidu et al., 2022).

Therapeutic Applications of Medicinal Plants in Neurological Disorders

Interest in medicinal plants as agents with potential therapeutic effects keeps growing as understanding of the link between neuroinflammation and neurological disorders grows. Growing evidence suggests that the bioactive compounds gotten from plants may provide a wide range of neuroprotective benefits by suppressing inflammatory responses, reducing oxidative stress, and regulating signaling pathways

that are associated with disease progression. Due to their multitarget mechanisms, medicinal plants have demonstrated therapeutic potential in several neurological and neurodegenerative disorders.

Alzheimer's Disease

Alzheimer's disease, the leading cause of dementia, has a characteristics of gradual memory loss, cognitive decline, and neuronal degeneration. Chronic neuroinflammation, oxidative stress, amyloid-β deposition, and tau hyperphosphorylation play important roles in disease progression (Heneka et al., 2015; Leng & Edison, 2021).

Several medicinal plants have shown potential in reducing the pathological changes that are associated with alzheimer's disease. Curcumin reduces neuroinflammation, oxidative stress, and amyloid-β aggregation, while epigallocatechin-3-gallate (EGCG) protects neurons and improves synaptic function (Hewlings & Kalman, 2017; Mandel et al., 2011). *Withania somnifera, Bacopa monnieri, Panax ginseng,* and *Zingiber officinale* have also shown beneficial effects in experimental models by improving cognitive function and reducing inflammatory and oxidative damage (Aguiar & Borowski, 2013; Kim et al., 2018; Kaur & Chugh, 2020).

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder that is progressive and characterized by the loss of dopaminergic neurons in the substantia nigra. In addition to motor symptoms such as tremor, rigidity, and bradykinesia, chronic neuroinflammation and oxidative stress contribute greatly to the disease progression (Bloem et al., 2021; Poewe et al., 2017).

Medicinal plants have demonstrated neuroprotective effects in experimental models of Parkinson's disease. Curcumin and epigallocatechin-3-gallate (EGCG) reduce oxidative stress, suppress microglial activation, and protect dopaminergic neurons from degeneration (Hewlings & Kalman, 2017; Mandel et al., 2011). Also, *Withania somnifera, Panax ginseng,* and *Zingiber officinale* have demonstrated anti-inflammatory and antioxidant activities that help improve the survival of neurons and motor function in preclinical studies (Kim et al., 2018; Kaur & Chugh, 2020; Semwal et al., 2015).

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. It is characterized by inflammation, demyelination, and progressive neuronal damage. Factors such as activated immune cells, excessive production of inflammatory cytokines, and oxidative stress contribute to myelin destruction and worsening neurological function (Reich et al., 2018; Filippi et al., 2018).

Curcumin, epigallocatechin-3-gallate (EGCG), and ginsenosides have been reported to inhibit inflammatory responses, reduce oxidative stress, and protect neurons in experimental models of Multiple sclerosis (Kaur & Chugh, 2020; Khan et al., 2021). *Withania somnifera and Zingiber officinale* have also shown immunomodulatory and antioxidant effects that may help reduce the severity of disease and aid in the improvement of neurological function (Semwal et al., 2015; Shen et al., 2024).

Ischemic Stroke

Ischemic stroke occurs when blood flow to the brain is interrupted which then leads to neuronal death, oxidative stress, and a very strong inflammatory response. Immediately cerebral ischemia occurs, microglia and astrocytes are being activated leading to the release of pro-inflammatory cytokines that worsens brain injury and impair neurological recovery (Campbell et al., 2019; Iadecola et al., 2020).

Curcumin, epigallocatechin-3-gallate (EGCG), ginsenosides, and gingerols attenuate neuroinflammation, oxidative stress, and neuronal apoptosis, which thereby improves neurological outcomes (Hewlings & Kalman, 2017; Kim et al., 2018; Shen et al., 2024). *Withania somnifera and Bacopa monnieri* have shown neuroprotective effects by preserving neuronal integrity and reducing inflammatory damage (Kaur & Chugh, 2020; Khan et al., 2021).

Depression and Neuropsychiatric Disorders

Evidence continues to show that neuroinflammatory mechanisms contribute immensely to the pathophysiology of depression and several neuropsychiatric disorders. An increase in the concentration of inflammatory cytokines and oxidative stress markers have been seen in individuals with depressive disorders (Miller and Raison, 2016).

Medicinal plants including Withania somnifera, Bacopa monnieri, and Panax ginseng have demonstrated neuroprotective and anti-inflammatory activities that may alleviate depressive symptoms and improve cognitive function (Dar et al., 2015; Kongkeaw et al., 2014). Their effects may involve regulation of inflammatory pathways and restoration of neurotransmitter balance.

Traumatic Brain Injury and Other Neurological Disorders

Traumatic brain injury (TBI) is a major cause of disability and is characterized by neuronal damage, oxidative stress, and persistent neuroinflammation. Once brain injury occurs, activated microglia and astrocytes releases inflammatory mediators that contribute to secondary brain damage and worsen neurological outcomes (Loane & Kumar, 2016; Simon et al., 2017).

Curcumin, epigallocatechin-3-gallate (EGCG), ginsenosides, and withanolides reduce neuroinflammation, oxidative stress, and neuronal apoptosis, thereby improving neurological recovery (Hewlings & Kalman, 2017; Kim et al., 2018; Shen et al., 2024). Neuroprotective effects by preserving neuronal function and reducing inflammatory damage are exhibited by *Bacopa monnieri and Zingiber officinale* (Aguiar & Borowski, 2013; Semwal et al., 2015).

Challenges and Limitations of Medicinal Plants in the Management of Neuroinflammation

A wide range of medicinal plants has shown anti-neuroinflammatory and neuroprotective activity in preclinical models. However, translating these findings into clinical use remains a major problem and setback.

A key limitation of medicinal plants is the poor bioavailability of many bioactive phytochemicals. Most of these compounds have physicochemical properties such as poor gastrointestinal absorption, rapid metabolism, low aqueous solubility and limited systemic distribution. Curcumin illustrates this problem very well. Despite its strong anti-inflammatory and antioxidant activity, its oral bioavailability is low because it is rapidly metabolized and poorly absorbed, which limits its therapeutic impact (Anand et al., 2007). Similarly, other plant-derived compounds such as polyphenols and flavonoids may exhibit reduced biological activity because of limited pharmacokinetic properties (Dai and Mumper, 2010).

Another major barrier is the blood-brain barrier (BBB). The BBB is a highly selective physiological barrier that regulates the entry of substances into the central nervous system and is essential for maintaining neural homeostasis. However, this same selectivity restricts the entry of many therapeutic compounds into the brain. Pardridge (2012) noted that poor BBB permeability continues to be a significant obstacle in developing effective therapies for neurological disorders. As a result, many bioactive constituents may not reach the concentration that is enough in the target brain regions to exert a therapeutic effect.

Standardization of medicinal plant preparations is another challenge. The phytochemical profile of a plant is not certain. It can differ based on plant species, geographical location, growing conditions, time of harvest, method of extraction, and also post-harvest storage. These variabilities can lead to inconsistencies in phytochemical content and therapeutic activity. According to Ekor (2014), lack of standardization may compromise reproducibility and quality control in herbal-based therapies.

Safety and toxicity considerations further complicate the use of medicinal plants. Although medicinal plants are frequently perceived as naturally safe alternatives, some plant extracts and phytochemicals may produce adverse effects, toxic reactions, or interactions with conventional medications. It was emphasized that inappropriate

dosage, prolonged use, and contamination with toxic substances may increase the risk of undesirable effects associated with herbal products (Posadzki et al., 2013).

In addition, most current and recent evidence about medicinal plants with anti-neuroinflammatory activities comes from experimental studies that involves cell cultures and animal models. Though these studies provide valuable insights, their findings may not always accurately predict clinical outcomes in humans. Differences in physiology, metabolism, and disease complexity may influence translational applicability of preclinical findings (Mak et al., 2014).

Despite these limitations, medicinal plants continue to represent valuable therapeutic resources because of their multitarget pharmacological activities and relative accessibility. Addressing current challenges through improved standardization procedures, advanced drug delivery systems, comprehensive toxicological assessments, and well-designed clinical studies may facilitate the successful translation of plant-derived compounds into clinical practice for the management of neuroinflammatory disorders.

Future Perspectives and Research Directions

The understanding of neuroinflammatory mechanisms keep increasing and new opportunities have been created for the development of plant-based interventions for neurological disorders due to the growing number of evidences that gives support to the therapeutic potential of medicinal plants. Numerous medicinal plants and their bioactive compounds have exhibited promising anti-neuroinflammatory effects in experimental studies but more research is still necessary in order to find solutions to the existing limitations and hasten their successful incorporation into clinical applications.

One important area that needs further investigation is the validation of preclinical findings through well-designed clinical studies. The most current evidence that demonstrate the anti-neuroinflammatory properties of medicinal plants was gotten from in vitro experiments and animal models. Though this studies have given substantial insight into molecular mechanisms and therapeutic activities, a major problem is the clinical efficacy and safety in human populations. In neurotherapeutic research, a significant challenge is the translational gap that is between preclinical investigations and clinical outcomes (Mak et al., 2014). Because of this, large-scale and randomized controlled trials are important to set strategies for appropriate dosing, long-term safety profiles, and therapeutic effectiveness.

Once there are advances in drug delivery technologies, there may be an improvement in the clinical utility of medicinal plant-derived compounds. Because of limited absorption, fast metabolism, and inadequate penetration across the blood-brain barrier, numerous phytochemicals show poor bioavailability. Compounds such as curcumin has significant pharmacological potential but under conventional administration methods, they are poorly available in the system (Anand et al., 2007). Approaches that are promising in improving drug stability, bioavailability, and targeted delivery to neural tissues have emerged. They are the nanotechnology-based delivery systems which includes nanoparticles, liposomes, nanoemulsions, and polymeric carriers. (Pardridge, 2012).

Further research should ensure there is more focus on identifying and characterizing novel bioactive compounds from medicinal plants with potential anti-neuroinflammatory properties. Improvements in analytical techniques such as metabolomics, proteomics, genomics, and high-throughput screening methods have enhanced the discovery of therapeutic molecules from natural sources. Such technologies may accelerate the identification of new compounds that are capable of targeting multiple pathways involved in neuroinflammation and neurodegeneration.

Another promising research direction is the combination therapy approach. Neuroinflammatory disorders involves a complex and interconnected pathological pathways, so a combination of plant-derived compounds with conventional pharmacological agents may produce synergistic therapeutic effects. Potentially this kind

of combination could improve the efficacy of treatment while reducing adverse effects that are associated with high-dose monotherapy. Previous studies have suggested that phytochemicals that has complementary biological activities may exert additive or synergistic effects of neuroprotection (Khan et al., 2021).

If precision medicine and personalized therapeutic approaches are applied, there may be a further enhancement of medicinal plant-based intervention effectiveness. Genetic variability, disease progression patterns, and individual responses to treatment can influence therapeutic outcomes. Medicinal plant research inclusion with personalized medicine strategies may improve the optimization of treatment and clinical outcomes in patients with neurological disorders.

Greater emphasis should be placed on standardization and quality control procedures for medicinal plant products. Differences in plant composition arising from environmental factors, cultivation conditions, harvesting practices, and extraction methods continues to affect how consistent therapeutic outcomes are. If the development of protocols for cultivation, extraction, and phytochemical characterization are being standardized there may be an improvement in the reliability and facilitation of regulatory approval of plant-derived therapeutic agents (Ekor, 2014).

Conclusion

Neuroinflammation plays a role in the pathogenesis of many neurological disorders thereby making it an important target for therapeutic intervention. This review has highlighted the growing evidence that supports the anti-neuroinflammatory potential of medicinal plants such as *Curcuma longa, Camellia sinensis, Withania somnifera, Bacopa monnieri, Panax ginseng, Zingiber officinale,* and *Waltheria americana*. The diverse bioactive compounds from these plants helps in modulating neuroinflammation by regulating the activation of glial, inhibiting inflammatory mediators, minimizing oxidative stress, and protecting neurons from injury.

The findings gotten from experimental studies are reassuring but there is limitation of clinical evidence for many plant-derived compounds. Poor bioavailability, lack of regulated herbal formulations, and insufficient clinical trials are the challenges that limits their translation into established medical practice. By addressing these limitations through in-depth pharmacological studies, well designed clinical trials, and standardized formulations, the therapeutic potential of medicinal plants will be fully realized.

Medicinal plants are a valuable source of novel bioactive compounds that may contribute to the development of safer and more effective approaches for the prevention and treatment of neuroinflammatory disorders.

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Author Contribution

This research was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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