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*Review Article*

# Neuroprotective effects of natural compounds on LPS-induced inflammatory responses in microglia

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**Abstract:** Neuroinflammation is one of the main mechanisms involved in the progression of neurodegeneration. The activation of microglia is the main feature of neuroinflammation, promoting the release of neurotoxic molecules and pro-inflammatory cytokines and resulting in the progressive neuronal cell death. Thus, suppression of the over-activation of microglia using novel pharmacological agents is an attractive issue to alleviate the neuroinflammatory processes associated with neurodegeneration. In recent years, medicinal plants-derived natural compounds have received extensive attention as useful sources of new neuroprotective agents for treating neurological disorders. In this review, we summarized the detailed research progress on the natural compounds derived from medicinal plants with potential anti-inflammatory effects and their molecular mechanisms on modulating the LPS-induced inflammatory responses in microglia. The natural compounds that efficacious in inhibiting the microglia activation include flavonoids, glycosides, phenolics, terpenoids, quinones, alkaloids, lignans, coumarins, chalcone, stilbene and others (biphenyl, phenylpropanoid, oxy carotenoid). They can reduce the expression of neurotoxic mediators (NO, PGE2, iNOS, COX-2) and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), down-regulate inflammatory markers and prevent neural damage. They exert anti-neuroinflammatory effects by modulating relevant signaling pathways (NF-κB, MAPKs, Nrf2/HO-1, PI3K/Akt, JAK/STAT) as demonstrated by experimental data. The present work reviews the role of microglia activation in neuroinflammation, highlighting the potential anti-inflammatory effects of natural compounds as a promising approach to develop innovative neuroprotective strategy.

**Keywords:** Natural compounds, neuroprotective, neuroinflammation, microglia

## Introduction

Neurodegenerative diseases are predicted to be the biggest health concern in this century and the second leading cause of death by 2050. Concomitant with the increase in longevity that has occurred over the past five decades, there has been a rise in the incidence of neurodegenerative disorders. Neurodegenerative diseases encompass a range of conditions in which neuronal structure and function are altered affecting the brain and spinal cord [central nervous system (CNS)] and worsening over time [1]. The main cellular and molecular events that cause neurodegeneration are oxidative stress, deposition of protein aggregates, neuroinflammation, impaired mitochondrial function, induction of apoptosis and alteration of autophagy [2]. Traditionally, the CNS has been considered as an immunologically privileged region and inflammation was viewed only as a passive response to neuronal damage. However, an increasing number of reports suggest that the CNS is immunologically specialized and inflammation plays an active role in neurodegenerative disease progression [3]. For a number of these neurodegenerative diseases, the initiating pathogenesis involves an inflammatory process in a response to a diverse array of CNS injuries, whose purpose is to protect and repair the tissues involved and restore homeostasis. A sustained inflammatory response or a change from acute to chronic neuroinflammation constitutes a fundamental process in the progression of several of these neurodegenerative diseases [4]. The CNS inflammatory response is orchestrated by an interaction of microglial cells, infiltrating myeloid cells, astrocytes, oligodendrocytes, the blood-brain barrier (BBB), and signaling molecules

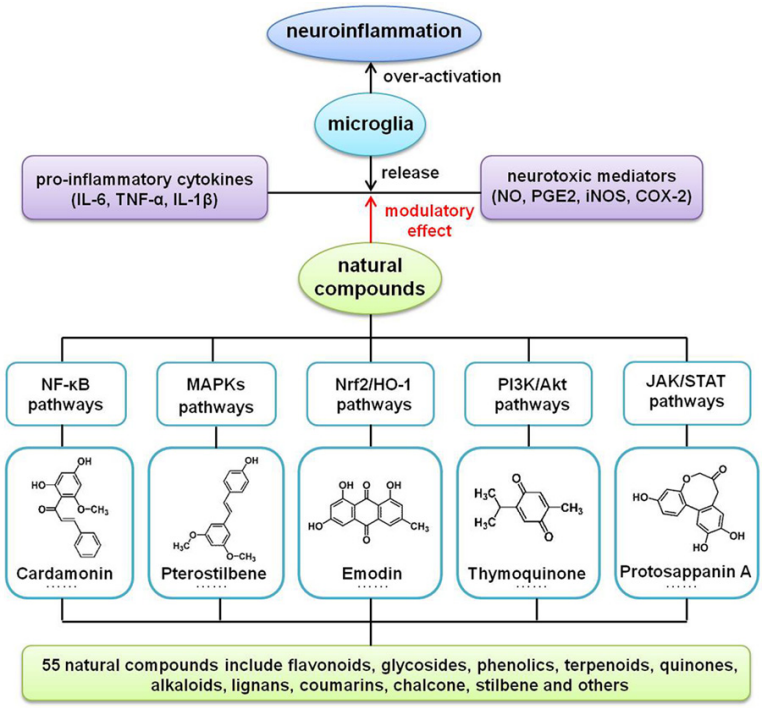



**Figure 1.** Schematic illustration showing the modulatory effects of natural compounds on LPS-induced inflammatory responses in microglia.

(cytokines, chemokines, and growth factors) that produces a reaction that is both central and peripheral [5].

Neuroinflammation is part of the immune response to harmful stimuli within the CNS. Its function is to remove necrotic cells and tissues induced by pathogens. Excessive neuroinflammation contributes to the progression of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [6]. The abnormal activation of microglia is the main feature of neuroinflammation, promoting the release of various neurotoxic mediators and pro-inflammatory cytokines and resulting in the progressive neuronal cell death [7, 8]. Therefore, rational modulation of microglia function to obtain neuroprotective effects is important for the development of safe and effective anti-inflammatory and neuroprotective agents [9].

To alleviate neuroinflammation, natural compounds have received extensive attention as useful sources of new therapeutic agents to treat neurological disorders [10]. Natural compounds are limited molecular weight (usually <3000 Daltons) organic molecules that were isolated from medicinal plants and also belong to "secondary metabolites" [11]. According to the physicochemical parameters of natural compounds reported in recent years, it has been concluded that these compounds tend to provide a higher degree of "drug-likeness" [12, 13]. Natural substances are rich in diverse bioactive with suited health benefits. Many plant species have been found to provide neuroprotective activity. Recently, increasing attentions have been given to natural compounds of plant origin with the potential neuroprotective effects of protecting the cells from neuroinflammation [10]. These small organic molecules are capable of interfering with protein-protein interactions and consequently affect cellular processes that possibly changed in disease states. These special characteristics have introduced natural compounds as valuable source of lead compounds in drug design projects [12, 14].

In recent years, an increasing number of researchers have attempted to search for efficient drugs for neurodegenerative diseases using natural compounds of plant origin. Considering the important role of neuroinflammation in the onset and development of neurodegenerative pathologies, the present review highlights the key inflammatory processes involved in neurodegeneration and the potentiality of medicinal-derived compounds to inhibit neuroinflammation in the CNS. We select the most recent and relevant data on the promising anti-neuroinflammatory role of natural compounds and their molecular mechanisms on inhibiting the microglia activation (**Figure 1**).

## Neuroinflammation: LPS-induced inflammatory responses in microglia

Inflammation is a biological defense response to eliminate stimulation of the areas affected by infection and cell damage. Neuroin-

flammation serves as a crucial defence against infectious agents in the CNS, which is caused by immune responses to pathogens or damaged cells within the brain. However, severe neuroinflammatory processes may result in neuronal damage observed in a number of neurodegenerative diseases [15].

Microglia are the unique resident immune cells of the CNS acting as primary mediators of inflammation. Although microglial density is region-specific, they comprise between 5 and 20% of all cells in the human brain, accounting for approximately 20% of the glial population [16]. Within healthy CNS tissue, microglia possess a unique ramified morphology with a small, round soma and numerous branching processes. Although long considered to be in a "resting" state, recent evidence indicates that ramified microglia have critical physiologic roles including determination of neuronal fate, migration, axonal growth, and synaptic remodeling during brain and spinal cord development. The critical contributions of microglia to CNS maturation can be attributed to their actions in phagocytosis of cellular debris, release of a variety of cell signaling factors including neurotrophins and extracellular matrix components, and direct contact with neurons [17].

Microglia also possess the necessary mechanism and characteristics to act as sensors for disruption in normal homeostasis within the mature CNS [18]. Microglia are rapidly activated following a number of pathologic events including altered neuronal function, infection, injury, ischemia, and inflammation. Activation results in a transition in microglia morphology to an ameboid state facilitating the migration of these cells to the site of insult [19]. Microglia response to CNS pathology also results in initiation of a number of immune functions including phagocytosis, antigen processing and presentation, and production of both cytotoxic and neurotrophic factors [20]. Microglial cells may undergo two different kinds of activation, acquiring a neurotoxic phenotype or a neuroprotective phenotype, which have been called M1-like and M2-like phenotypes respectively by their analogy with phenotypes in peripheral macrophages. Whereas M1-like microglia generate a detrimental microenvironment for neurons by producing inflammatory cytokines and reactive oxygen species (ROS), M2-like microglia secrete neurotrophic factors and anti-inflammatory mediators, thus inducing a supportive microenvironment for neurons [21]. Under physiological conditions, microglia are involved in immune surveillance and host defense against infections [22]. However, under neuroinflammatory conditions, abnormal activation of microglia can cause brain tissue damage by releasing various neurotoxic mediators, including reactive oxygen and nitrogen species (superoxide anion, nitric oxide), arachidonic acid metabolites (eicosanoids), excitotoxic glutamate, quininic acid, and histamine [23]. While short-term microglia activation is generally accepted to serve a neuroprotective role, chronic activation has been implicated as a potential mechanism in neurodegenerative disorders [24].

Activated microglia are considered to be an important hallmark of brain inflammation, and plays a key role in regulating neuroinflammatory reactions [19]. Hyperactive microglia are known to release a variety of neurotoxic mediators, such as nitric oxide (NO), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and a series of pro-inflammatory cytokines including tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), which further lead to neurodegenerative disorders [25]. PGE2 is an arachidonic acid derivative, the production of which is catalysed by cyclooxygenases in activated microglia. Cyclooxygenases are of two subtypes, cyclooxygenase-1 (COX-1) and COX-2. COX-1 is constitutively expressed in most cell types, whereas expression of COX-2 is induced by various factors including inflammatory cytokines, and is mainly responsible for the production of PGE2 [26]. In cultured rat brain microglia, bacterial LPS has been shown to induce COX-2 expression, and this is prevented in the presence of inhibitors of NF-κB [27]. In addition to PGE2, the cellular messenger NO has been widely implicated in neuroinflammation and neurodegenerative processes. Elevated levels of NO has been reported in both microglia and astroglia, which are activated during the neuroinflammatory response [28]. Significant body of evidence also suggests that the release of large amounts of NO from activated astrocytes and microglia, mediated by the iNOS, is important in the pathogenesis of neurodegenerative disorders. This is evident in the induction of neuronal death through both necrotic and apoptotic pathways [28]. Consequently, both COX-2-mediated PGE2 and iNOS-mediated NO

production in the microglia remain important targets in reducing neuroinflammation in the microglia. TNF-α is a proinflammatory cytokine that exerts both homeostatic and pathophysiological roles in the CNS. In pathological conditions, microglia release large amounts of TNF-α, this de novo production of TNF-α is an important component of the neuroinflammatory response that is associated with several neurological disorders system [29]. Interleukin-1 (IL-1) is one of the most well-known proinflammatory cytokines that act within the brain during different insults and neurodegenerative diseases. The IL-1 system involves two essential agonists, IL-1 alpha (IL-1α) and IL-1 beta (IL-1β), as well as the endogenous antagonist, IL-1 receptor antagonist (IL-1ra) [30]. Both IL-1α/β exert similar biological effects by binding to IL-1 receptor 1 (IL-1R1), whereas IL-1ra blocks IL-1α/β biological activity by competing with them by binding to IL-1R1 [30, 31]. Microglia appear to be the main cells in the brain that express the IL-6 receptor and potently secrete IL-6 during peripheral immune stimulation [32]. IL-6 knockout (IL-6-/-) mice have shown an overall decrease in the number of activated brain macrophages associated with cortical lesions, suggesting a role for IL-6 in the orchestration of central nervous system inflammation [33].

Lipopolysaccharides (LPS) are endotoxins composed of O-antigen which are found in gram negative bacteria outer membrane, have been reported as most potent stimuli for the microglial activation [34]. Toll like receptor 4 (TLR4), an important pattern recognition receptor (PRR), is expressed by microglial cells [35] and is responsible for inflammatory cascade in microglia upon binding with LPS. Members of the TLR family play critical roles as regulators of innate and adaptive immune responses [36]. To date, 11 human TLRs and 13 murine TLRs have been identified [35]. TLR4, an important member of TLR family, is highly expressed on macrophages and microglia and is able to recognize LPS associated with gram-negative bacteria [37]. Once LPS binds to TLR4 on the surface of microglia, it leads to the activation of several signal transduction pathways of inflammatory processes [38]. Activated TLR4 transfers the signal through the two main downstream pathways: First, the TLR4-mediated myeloid differentiation factor 88 (MyD88)-dependent pathway and second, the Toll/IL-1 receptor domain-containing adapter induction of the interferon-β (TRIF)-dependent pathway [38]. MyD88 is an adapter protein which mediates signaling pathways for most TLRs, which leads to activation of NF-κB and MAPKs [39].

## Neuroprotective effects of natural compounds on LPS-induced inflammatory responses in microglia

### *Modulatory effects of natural compounds on NF-κB and/or MAPK pathways*

*NF-κB and MAPK signaling pathways:* Nuclear factor-kappa B (NF-κB), a major transcription factor, modulates inflammatory system through expressing proinflammatory genes including iNOS and COX-2 [40]. Under normal conditions, NF-κB is resident as an inactivation form complex with inhibitors of κB (IκB) in the cytoplasm. The activation of NF-κB requires phosphorylation of upstream IκB kinase (IKK), which contains two catalytic subunits, IKKα and IKKβ [41]. Upon stimuli with LPS and proinflammatory cytokines, IKK is phosphorylated and activated via upstream of TGF-β activated kinase 1 (TAK1), resulting in further phosphorylation and degradation of IκB in the ubiquitination pathway [42]. Then, NF-κB releases from the IκB/NF-κB dimer and translocates from cytoplasm into the nucleus and binds to the DNA binding site related to regulating the transcriptions of its target genes, inducing further proinflammatory gene expression and inflammatory response [43]. Therefore, the inhibition of the NF-κB pathway may have a potential therapeutic effect in neurodegenerative diseases that are accompanied by microglial activation.

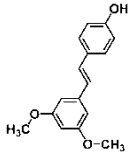
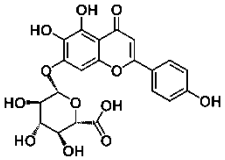
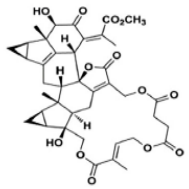
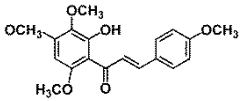
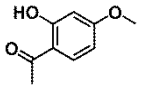
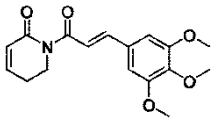
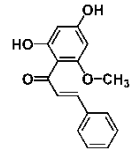
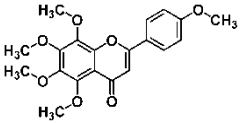
Mitogen-activated protein kinases (MAPKs), as another major inflammatory signal, are also involved in regulating the expression of several inflammatory genes. MAPK family plays a crucial role in transducing a variety of extracellular signals to the nucleus. Both in vitro and in vivo studies have shown that activation of MAPKs (ERK, JNK, and p38) is necessary for a number of the inflammatory responses to LPS [44]. For example, p38 and JNK MAPKs activities are strongly enhanced in multiple cell types including glial cells, endothelial cells, and as well as mononuclear macrophages by LPS or inflammatory cytokines through increasing their phosphorylation levels, and further accelerate inflammatory responses; moreover, TNF-α mRNA

transport from the nucleus to the cytoplasm could be blocked by ERK inhibitor [45]. Therefore, MAPKs pathway may act as an important drug target for anti-inflammation therapy.

*Natural compounds acting on NF-κB and/or MAPK pathways:* The plant-derived natural compounds that exerted anti-neuroinflammatory effects on LPS-activated microglia via inhibition of NF-κB or MAPK signaling pathways include pterostilbene, scutellarin, shizukaol B, 2'-hydroxy-4,3',4',6'-tetramethoxychalcone, paeonol, piperlongumine, cardamonin, tangeretin, thymoquinone, chrysin, formononetin, gomisin A, steppogenin, hyperoside, anisalcohol, (5-formylfuran-2-yl) methyl 4-hydroxy-2-methylenebutanoate, scoparone, pseudoginsenoside-F11, 20C, lonchocarpine, schisandrin B, obovatol, icariin, deoxysappanone B, tiliroside, MC13, schizandrin A and DSF-52 (**Table 1**).

MAPKs are proved to be important upstream signaling molecules for regulating secretion of proinflammatory mediators. Pterostilbene is a stilbene found in berries, grapes and grape vine. Pterostilbene exerted anti-neuroinflammatory effect on LPS-activated microglia via inhibition of MAPK signaling pathways [46]. Scutellarin is a flavone and the major active component of *Erigeron breviscapus* (Vant.) Hand-Mazz. Scutellarin exerted anti-inflammatory effects in LPS-activated BV2 microglia through regulation of MAPKs signaling pathway [47]. MAPKs are upstream of the transcription factors NF-κB and AP-1, which both control the expression of inflammatory mediators including iNOS, COX-2, IL-1β and TNF-α. JNK activation induces the phosphorylation of c-Jun, which then causes the activation of AP-1 [48]. Shizukaol B is an active sesquiterpene isolated from the whole plant of *Chloranthus henryi*. Shizukaol B exerted anti-inflammatory effects in LPS-activated microglia partly by modulating JNK/AP-1 signaling pathway [49]. NADPH oxidase is the major enzyme for the production of ROS in immune cells and is highly expressed in microglia. NADPH oxidase is a significant source of intracellular ROS during neuroinflammation. NADPH oxidase-dependent ROS production accelerates neuroinflammatory processes and contributes to various inflammation-associated neurodegenerative diseases [50]. 2'-hydroxy-4,3',4',6'-tetramethoxychalcone (HTMC) is a known chalcone derivative isolated from *Chloranthus henryi*. HTMC suppressed inflammatory responses in LPS-stimulated BV2 microglial cells by modulating JNK/AP-1 and NADPH oxidases-ROS pathways [51]. Paeonol is a phenolic compound extracted from *Moutan cortex*. In LPS-treated primary microglia, paeonol attenuated the overexpression of iNOS and COX-2, leading to the decrease in NO and PGE2 production, respectively. Further study indicated that paeonol suppressed the inflammatory responses by modulating JNK, ERK and NADPH oxidases-ROS pathways [52]. Piperlongumine is an alkaloid extracted from *Piper longum*. Piperlongumine significantly inhibited the production of NO and PGE2 induced by LPS. Piperlongumine also reduced the expression of iNOS and COX-2 as well as proinflammatory cytokines such as TNF-α and IL-6. Piperlongumine exerted anti-neuroinflammatory effects by suppressing the NF-κB signaling pathway in LPS-stimulated BV2 microglia cells [53]. Cardamonin is a chalcone isolated from *Alpinia rafflesiana*. Cardamonin inhibited inflammatory responses in interferon-γ (IFN-γ)/LPS-stimulated BV2 microglia via NF-κB signaling pathway [54]. Tangeretin is a flavonoid from citrus fruit peels. Tangeretin exerted anti-neuroinflammatory effects via NF-κB modulation in LPS-stimulated microglial cells [55]. Thymoquinone has been identified as benzoquinone compound of the natural product *Nigella sativa* seed oil. Thymoquinone treatment of LPS/IFN-γ-activated BV2 microglial cells induced a significant increase in expression of neuroprotective proteins (biliverdin reductase-A, 3-mercaptopyruvate sulfurtransferase, glutaredoxin-3, and mitochondrial lon protease), a significant decrease in expression of inflammatory cytokines, and a decrease in the expression of signaling target genes of the NF-κB pathway [56]. Chrysin is a natural, biologically active flavonoid compound obtained from honey, propolis and plants. Chrysin inhibited NF-κB pathway and TRAF6 (TNF-receptor-associated factor 6) expression, but upregulated the expression of zinc-finger protein A20. Further studies had revealed upregulation of A20 could regulate the inhibitory effects of chrysin on NF-κB pathways via regulation of TRAF6 polyubiquitination. The present study demonstrated that chrysin exerted anti-neuroinflammatory effect via a novel mechanism, the upregulation of A20 expression, also validated A20 was a novel effective pharmacological target for developing agents

**Table 1.** The category, sources, structure, dose, effects and mechanisms of 28 natural compounds acting on NF-κB/MAPKs pathways

| Natural compound | Category | Sources | Structural formula | Dose | Cell lines | Effects and Mechanisms | Refrence |
|---|---|---|---|---|---|---|---|
| Pterostilbene | stilbenes | berries, grapes and grape vine |  | 1, 3, 10, 30 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, NO, IL-6, TNF-α); ↓ MAPKs signaling | [46] |
| Scutellarin | flavone | *Erigeron breviscapus* |  | 0.54 μM | LPS-activated BV2 microglia | ↓ (iNOS, TNF-α, IL-1β); modulate MAPKs signaling | [47] |
| Shizukaol B | sesquiterpene | *Chloranthus henryi* |  | 12.5, 25, 50 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, NO, TNF-α, IL-1β); modulate JNK/AP-1 signaling | [49] |
| 2'-hydroxy-4,3',4',6'-tetramethoxychalcone (HTMC) | chalcone derivative | *Chloranthus henryi* |  | 6.25, 12.5, 25 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, NO, TNF-α, IL-1β, IL-6; ROS); modulate JNK/AP-1 and NADPH oxidases-ROS pathways | [51] |
| Paeonol | phenolic | *Moutan cortex* |  | 0.75, 1, 1.5 μM | LPS-stimulated primary microglia | ↓ (iNOS, COX-2, NO, PGE2); modulate JNK, ERK and NADPH oxidases-ROS pathways | [52] |
| Piperlongumine | alkaloid | *Piper longum* |  | 0.2, 1, 5 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, NO, PGE2, TNF-α, IL-6); ↓ NF-κB pathway | [53] |
| Cardamonin | chalcone | *Alpinia rafflesiana* |  | 2, 10, 50 μM | IFN-γ/LPS-stimulated BV2 microglia | ↓ (NO, PGE2, TNF-α, IL-1β, IL-6, iNOS, COX-2); ↓ NF-κB pathway | [54] |
| Tangeretin | flavonoid | citrus fruit peels |  | 80 μM | LPS-stimulated primary/BV2 microglia | ↓ (NO, PGE2, TNF-α, IL-1β, IL-6, iNOS, COX-2); ↓ NF-κB and MAPK signaling | [55] |

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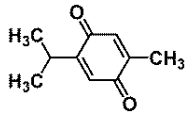
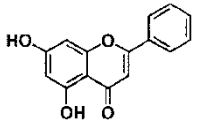
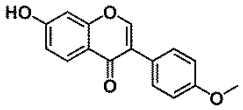
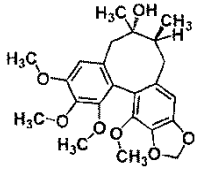
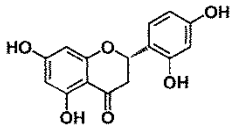
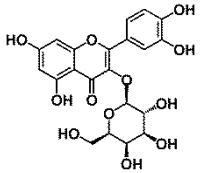
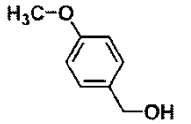
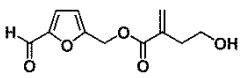
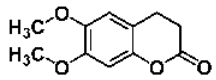
|---|---|---|---|---|---|---|---|
| Thymoquinone | benzoquinone | *Nigella sativa* seed oil |  | 12.5 μM | LPS/IFN-γ-activated BV2 microglia | ↑ neuroprotective proteins;<br>↓ inflammatory cytokines;<br>↓ NF-κB pathway | [56] |
| Chrysin | flavonoid | honey, propolis and plants |  | 5, 10 μM | LPS-activated BV2 microglia | ↓ NF-κB pathway and TRAF6 expression;<br>↑ zinc-finger protein A20 | [57] |
| Formononetin | non-steroidal polyphenol | red clover |  | 2.5, 5, 10 mM | LPS-activated BV2 microglia | ↓ (TNF-α, IL-6, IL-1β, nitrite, PGE2; iNOS, COX-2); ↑ ERβ;<br>↓ NF-κB signaling pathway | [58] |
| Gomisin A | dibenzocyclooctadiene lignans | *Schisandra chinensis Baill* |  | 3, 10, 30, 100 μM | LPS-stimulated N9 microglia | ↓ (iNOS, COX-2, NO, PGE2, TNF-α, IL-1β, IL-6; ROS, NADPH oxidase, gp91phox);<br>↓ NF-κB and MAPKs pathways | [59] |
| Steppogenin | flavonoid | *Cudrania tricuspidata* |  | 10, 20, 40, 80 μM | LPS-stimulated BV2/primary microglia | ↓ proinflammatory mediators and cytokines<br>↓ NF-κB and MAPK pathways | [60] |
| Hyperoside | galactoside | *Acanthopanax senticosus; Hypericum perforatum* |  | 2.5, 5, 10, 20 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, NO, IL-1β, TNF-α);<br>↓ p38 and NF-κB pathways | [61] |
| Anisalcohol | phenolic | *Gastrodia elata Blume* |  | 0.01, 0.1, 1 μM | LPS-stimulated BV2 microglia | ↓ (TNF-α, PGE2, NO); modulate microglia polarization;<br>↓ NF-κB p65 and JNK activation | [63] |
| (5-formylfuran-2-yl) methyl 4-hydroxy-2-methylenebutanoate | esters | *Polygala tricornis Gagnep* |  | 2.5, 5, 10 μM | LPS-induced BV2 microglia | AR inhibitor<br>↓ inflammatory mediators;<br>↓ PLC/PKC-dependent NF-κB and MAPK pathways | [64] |
| Scoparone | coumarin | *Castanea crenata* |  | 100, 250, 500 μM | LPS-stimulate BV2 microglia | ↓ proinflammatory cytokine;<br>↓ IRF3 and ERK signaling | [66] |

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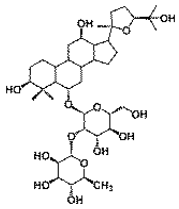
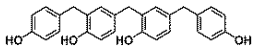
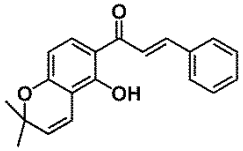
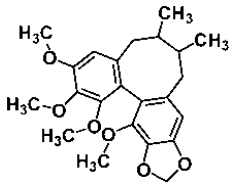
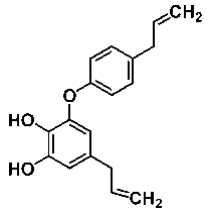
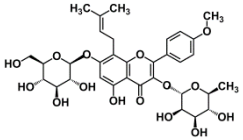
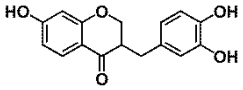
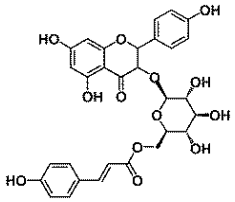
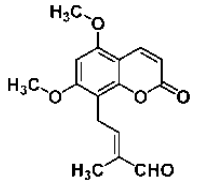
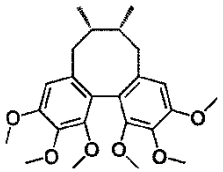
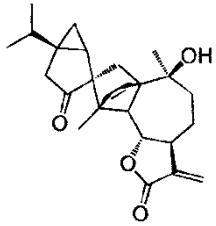
|---|---|---|---|---|---|---|---|
| Pseudoginsenoside-F11 | ocotillol-type ginsenoside | *Panax quinquefolium* L. |  | 1, 3, 10, 30, 100 μM | LPS-activated N9 microglia | ↓ (ROS, proinflammatory mediators);<br>↓ TLR4-mediated TAK1/IKK/NF-κB, MAPKs and Akt pathways | [67] |
| 20C | bibenzyl | *Gastrodia elata* |  | 0.1, 1, 10 μM | LPS-activated BV2 microglia | ↓ (iNOS, COX-2, IL-1β, NO, TNF-α);<br>↑ autophagy-related proteins<br>↓ MAPKs, TLR4/Akt/mTOR signaling | [68] |
| Lonchocarpine | phenylpropanoid | *Abrus precatorius* |  | 5, 10, 20 μM | LPS/poly(I:C)-stimulated BV2 microglia | ↓ (iNOS, proinflammatory cytokines);<br>↓ MyD88/IRAK4-TAK1-NF-κB signaling | [69] |
| Schisandrin B | lignans | *Schisandra chinesnesis* |  | 5, 10, 20 μM | LPS-induced primary microglia, microglia-neuron co-cultures | ↓ (proinflammatory cytokines, ROS, NADPH oxidase activity);<br>↓ TLR4-dependent MyD88/IKK/NF-κB signaling | [71] |
| Obovatol | neolignans | *Magnolia obovata* |  | 10 μM | LPS-induced BV2 microglia | ↓ (proinflammatory cytokines, NO, iNOS);<br>↑ ROS-scavenging activity of Prx2;<br>↓ NF-κB, STAT1, MAPK | [72] |
| Icariin | flavonoid | *Epimedium brevicornum* |  | 5, 10, 50 μM | LPS-induced primary microglia | ↓ (NO, PGE2, ROS, TNF-α, IL-1β, IL-6, iNOS, COX-2);<br>↓ TAK1/IKK/NF-κB and JNK/p38 MAPK pathways | [73] |
| Deoxysappanone B | homoisoflavone | *Caesalpinia sappan* L. |  | 10, 20, 50 μM | LPS-induced BV2 microglia, neuron-microglia co-cultures | ↓ (NO, PGE2, ROS, TNF-α, IL-6);<br>↓ IKK-NF-κB and p38/ERK MAPK pathways | [74] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Tiliroside | glycosidic flavonoid | linden, rose hip, strawberry |  | 2, 4, 6 μM | LPS-stimulated BV2 microglia | ↓ (TNF-α, IL-6, NO, PGE2, iNOS, COX-2); ↓ TRAF6-mediated NF-κB and p38 MAPK pathways | [76] |
| MC13 | coumarin | Murraya |  | 10, 20, 50 μM | LPS-induced BV2 microglia | ↓ inflammatory mediators; ↓ TRAF6-TAK1-NF-κB, p38/ERK MAPKs and JAK2-STAT1/STAT3 pathways | [79] |
| Schizandrin A | lignan | *Schisandra chinesnesis* |  | 10, 20, 50 μM | LPS-induced BV2/ primary microglia | ↓ (NO, TNF-α, IL-6, iNOS, COX-2); ↓ TRAF6-IKKβ-NF-κB and JAK2-STAT3 pathways | [80] |
| DSF-52 | sesquiterpene dimer | *Artemisia argyi* |  | 2.5, 5, 10 μM | LPS-activated microglia | ↓ (iNOS, COX-2, NO, PGE2, TNF-α, IL-1β, GM-CSF and MIP-1α); ↑ IL-10; ↓ NF-κB, JNK/p38 MAPKs and JAK2/STAT3 pathways | [81] |

in the treatment of neuroinflammation-related diseases [57]. Formononetin is a bioactive non-steroidal polyphenol found in a variety of plants. Formononetin significantly reduced the production of TNF-α, IL-6 and IL-1β, nitrite and PGE2, as well as protein levels of iNOS and COX-2. The study established that formononetin inhibited neuroinflammation by targeting NF-κB signaling pathway in BV2 microglia, possibly through mechanisms involving ERβ [58]. Gomisin A is one of the major dibenzocyclooctadiene lignans isolated from *Schisandra chinensis* Baill. Gomisin A inhibited LPS-induced inflammatory responses in N9 microglia via blocking the NF-κB/MAPKs pathway [59]. Steppogenin is a flavonoid compound isolated from *Cudrania tricuspidata*. The study suggested that steppogenin exerted anti-neuroinflammatory effects against acute neuroinflammation in LPS-stimulated BV2 and rat primary microglial cells by suppressing the activation of NF-κB and MAPK signaling and the production of proinflammatory mediators and cytokines [60]. Hyperoside is a galactoside isolated from *Acanthopanax senticosus* and *Hypericum perforatum*. Hyperoside inhibited LPS-induced inflammatory responses in BV2 microglial cells via p38MAPK and NF-κB pathways [61]. It is now well recognized that microglia have functional plasticity and dual phenotypes, proinflammatory M1 and anti-inflammatory M2 phenotypes. Inhibiting the M1 phenotype or stimulating the M2 phenotype has been suggested as a potential therapeutic approach for the treatment of neuroinflammation-related diseases [62]. Anisalcohol is a phenolic compound isolated from *Gastrodia elata* Blume. Anisalcohol showed anti-inflammatory effects on LPS-stimulated BV2 microglia via selective modulation of microglia polarization and down-regulation of NF-κB p65 and JNK activation [63]. (5-formylfuran-2-yl) methyl 4-hydroxy-2-methylenebutanoate (FMHM) is a naturally derived aldose reductase (AR) inhibitor that isolated from *Polygala tricornis Gagnep*. Zeng's study suggested that AR was a potential target for neuroinflammation inhibition and FMHM displayed anti-neuroinflammatory efficacy via phospholipase C/protein kinase C (PLC/PKC)-dependent NF-κB and MAPK pathways [64]. TLR4 transduces the phosphorylation of the two adaptor proteins TRIF (Toll/IL-1 receptor domain-containing adapter induction of the interferon-β) and MyD88 downstream. LPS-stimulated TRIF-dependent signaling induces the transcription factor, interferon regulatory factor 3 (IRF3); otherwise, MyD88-dependent signaling transduces another type of transcription factor, NF-κB. Also, IRF3 plays an important role in the innate immune system's response to viral infection [65]. Scoparone is a coumarin found in the inner shell of *Castanea crenata*. Scoparone inhibited LPS-simulated inflammatory response by suppressing IRF3 and ERK in BV2 microglial cells [66]. Stimulation of the TLR4 extracellular domain by LPS sequentially triggers the intracellular association of MyD88 with its cytosolic domain. Therefore, MyD88 serves as a key TLR4 adaptor protein, linking the receptors to downstream kinases, suggesting that TLR4 and MyD88 act as specific targets for inflammatory responses. Pseudoginsenoside-F11 is an ocotillol-type ginsenoside contained in *Panax quinquefolium* L. Pseudoginsenoside-F11 exerted anti-neuroinflammatory effects on LPS-activated microglial cells by inhibiting TLR4-mediated TAK1/IKK/NF-κB, MAPKs and Akt signaling pathways [67]. 20C is a novel bibenzyl compound isolated from *Gastrodia elata.* 20C significantly attenuated the protein levels of iNOS and COX-2, and secretion of NO, IL-1β and TNF-α induced by LPS in BV2 cells. 20C exerted anti-neuroinflammatory effects via regulating autophagy in LPS-activated BV2 cells through MAPKs and TLR4/Akt/mTOR signaling pathways [68]. Lonchocarpine is a natural phenylpropanoid compound isolated from *Abrus precatorius.* Lonchocarpine suppressed the expression of iNOS and proinflammatory cytokines in LPS or poly(I:C)-stimulated BV2 microglial cells. It was suggested that TLR4 downstream signals such as MyD88/IRAK4-TAK1-NF-κB were at least partly involved in the anti-inflammatory mechanism of lonchocarpine in LPS-stimulated microglia [69]. Microglia consistently generate ROS when activated by multiple immunological stimuli, which can induce neuronal degeneration. It has been demonstrated that LPS induces production of ROS via NADPH oxidase activation and leads to activation of NF-κB, MAPKs, STAT and secretion of proinflammatory cytokines [70]. Schisandrin B is a lignan compound isolated from the Schizandra fruit (*Schisandra chinesnesis*). Schisandrin B exerted neuroprotective activity by attenuating the microglia-mediated neuroinflammatory response by inhibiting the TLR4-dependent MyD88/IKK/NF-κB signaling pathway.

Furthermore, schisandrin B inhibited the production of ROS and NADPH oxidase activity in microglia [71]. Obovatol is a lignan compound from the leaves of *Magnolia obovata*. Obovatol attenuated microglia-mediated neuroinflammation by modulating redox regulation. Obovatol targeted cellular Prx2 protein in order to increase its ROS-scavenging activity. As ROS were the pivotal component of inflammatory signaling of microglia, obovatol-mediated reduction of ROS led to the inhibition of multiple inflammatory signaling pathways such as NF-κB, STAT1, and MAPKs in microglia [72]. Icariin is a flavonoid compound from *Epimedium brevicornum* Maxim. Icariin attenuated LPS-induced microglial activation and resultant death of neurons by inhibiting TAK1/IKK/NF-κB and JNK/p38 MAPK pathways [73]. Deoxysappanone B is a homoisoflavone compound isolated from *Caesalpinia sappan*. Deoxysappanone B protected neurons from microglia-mediated inflammatory injuries via inhibition of IKK/NF-κB and p38/ERK MAPK pathways [74]. Upon LPS stimulus, TLR4/MyD88 induces the expression of iNOS, COX-2 and the proinflammatory cytokines, through TRAF6-dependent activations of both NF-κB signaling pathway. Furthermore, LPS-induced activation of TRAF6 is one of the most important events upstream of the IKKα/IκB-NF-κB inflammatory signaling pathway. In addition to NF-κB activation, TLR can also initiate MAPK signaling cascades and activate multiple transcription factors, following LPS activation. TRAF6 can activate the MAPK kinase MKK3/6, which in turn activates p38 [75]. Tiliroside is a glycosidic flavonoid found in several medicinal and dietary plants, such as linden, rose hip and strawberry. Tiliroside inhibited neuroinflammation in BV2 microglia through a mechanism involving TRAF6-mediated activation of NF-κB and p38 MAPK signaling pathways [76]. NF-κB transcriptional activity is required for TLR4-mediated interaction of TRAF6 with TAK1. TAK1-binding protein 2 (TAB2) is an adaptator protein that brigdes TRAF6 to TAK1, promoting TAK1 activation and subsequent IKK degradation and NF-κB activation [77]. Direct LPS stimulation and LPS-induced production of IFN-γ and IL-6, which subsequently activate Janus kinase 2 (JAK2)-STAT1 (signal transducers and activators of transcription 1) and STAT3 signaling pathways, are important events for microglia-dependent neuroinflammatory process. A negative regulation in JAK2 can effectively down-regulate STAT3 activity and suppress inflammatory mediator release [78]. MC13 is a novel coumarin compound found in Murraya, an economic crop whose leaves are widely used as condiment (curry) in cuisine. MC13 protected neurons from microglia-mediated neuroinflammatory injury by inhibiting TRAF6-TAK1-NF-κB, p38/ERK MAPKs, and JAK2-STAT1/3 pathways [79]. Schizandrin A is a lignan compound isolated from *Schisandra chinesnesis*. Schizandrin A exerted anti-inflammatory and neuroprotective effects by alleviating microglia-mediated neuroinflammation injury through inhibiting the TRAF6-IKKβ-NF-κB and JAK2-STAT3 signaling pathways [80]. DSF-52 is a novel sesquiterpene dimer compound isolated from medical plant *Artemisia argyi*. DSF-52 inhibited microglia-mediated neuroinflammation via suppression of NF-κB, JNK/p38 MAPKs and JAK2/STAT3 signaling pathways [81].

*Modulatory effects of natural compounds on Nrf2/HO-1 signaling pathway*

*Nrf2/HO-1 signaling pathway*: Reactive oxygen species (ROS) are produced for the maintenance of many physiological functions and act as second messengers. However, accumulating evidence has suggested that the pathogenesis of neurodegenerative disorders is related to excessive production of ROS and the resultant increased oxidative stress [82]. Increased ROS production has been shown to control the expression of several inflammatory mediators. Oxidative stress is also responsible for the expression of critical inflammatory target proteins such as COX-2, iNOS and the adhesion molecules induced by cytokines, infections and peptides. Furthermore, microglia cells are known to release different inflammatory mediators in response to oxidative stress [83]. The nuclear factor erythroid 2 related factor 2 (Nrf2) is a critical regulator of endogenous inducible defence systems in the body. Under physiological conditions, Nrf2 is mainly located in the cytoplasm. However, in response to oxidative stress, Nrf2 undergoes nuclear translocation and binds to specific DNA sites known as the antioxidant response elements (ARE), to initiate transcription of cytoprotective genes [84]. The relationship between Nrf2 and NF-κB is not well-understood. However, NF-κB has been shown to attenuate the transcription

of genes that are under the control of Nrf2 [85]. Taken together, there appears to be a crosstalk between these transcription factors in neuroinflammation.

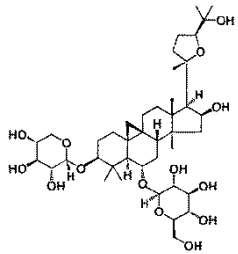
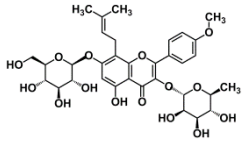
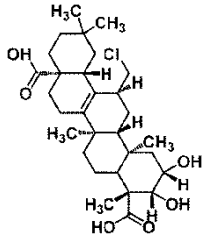
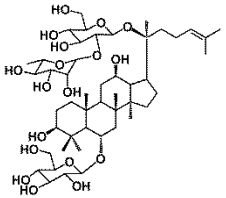
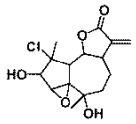
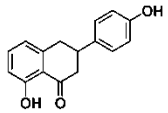
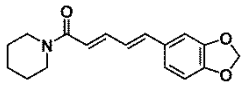
Nrf2 is a transcription factor of the Cap 'n' collar family, which regulates the production of various anti-oxidative enzymes. Nrf2 not only plays protective roles against oxidative stress in a number of organs, but also negatively regulates inflammatory responses [86]. Nrf2 activation attenuates the sustained neuroinflammatory response, and protects neighbor neuronal cells against LPS and amyloid beta-induced microglial activation. The Nrf2/ARE signaling pathway is a well-known cellular pathway involving anti-oxidative responses that activates downstream signaling by phase II enzymes such as HO-1 and NQO1. In addition, the upregulation of Nrf2/ARE-related phase II enzymes, including HO-1 and NQO1, has inhibitory effects on the abnormal neuroinflammatory response. Nrf2/ARE signaling is activated during the early phase of neuroinflammatory response [87].

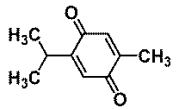
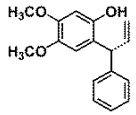
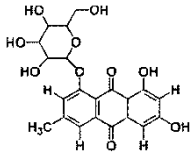
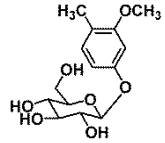
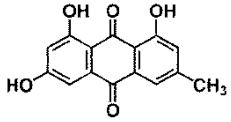
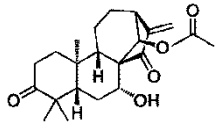
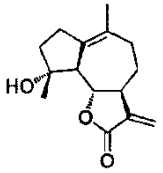
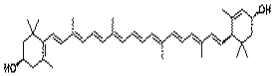
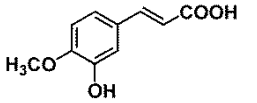
Heme oxygenase-1 (HO-1), alternatively referred to as HSP32, belongs to the HSP family, and is an inducible enzyme that acts against oxidative stress by degrading heme into three byproducts-biliverdin, carbon monoxide, and free iron. HO-1 and the enzymatic byproducts appear to play an important role in anti-inflammatory responses. The HO-1 signaling pathway is associated with the anti-oxidants NQO1 and glutathione-S transferase in the neuroinflammatory response. Recent reports have shown that neuroinflammatory signaling induces HO-1 and NQO1 expression, and the induction of HO-1 and NQO1 inhibits iNOS and COX-2 expression in LPS-induced microglia [86, 88]. Additionally, HO-1 expression is tightly regulated by Nrf2 via direct binding of Nrf2 to AREs of HO-1 [89]. Consistent with these findings, several experiments targeting Nrf2-mediated HO-1 expression have shown a beneficial effect against various inflammatory animal models [90].

*Natural compounds acting on Nrf2/HO-1 signaling pathway:* The plant-derived natural compounds that inhibited LPS-induced inflammatory responses in microglia via activating the Nrf2-mediated HO-1 signaling pathway include astragaloside IV, icariin, tenuigenin, ginsenoside Rg18, andalucin, hydrangenol, piperine, thymoquinone, 9-Hydroxy-6,7-dimethoxydalbergiquinol, CRPE56IGIH, CRPE55IB, emodin, glaucocalyxin B, micheliolide, lutein and trans-isoferulic acid (**Table 2**).

HO-1 acts as a rate-limiting enzyme in most cell lines. Nrf2 is a master regulator of detoxifying/antioxidant phase II enzymes, including HO-1. HO-1 is included in the family of AREs-containing genes and regulates Nrf2. Astragaloside IV is one of the main active ingredients in *Radix Astragali*. Astragaloside IV significantly reduced the production of inflammatory mediators NO, TNF-α and IL-6 in LPS-induced BV2 and primary microglial cells. Further research demonstrated that the activation of Nrf2/HO-1 via ERK signaling pathway was a novel mechanism of astragaloside IV which exerted anti-neuroinflammatory activity in microglia cells [91]. New findings have linked activation of Nrf2 signaling to anti-inflammatory effects. Icariin is a natural compound derived from *Herba Epimedii*. Icariin suppressed LPS-induced microglial pro-inflammatory factors production. In addition, activation of Nrf2 signaling pathway participated in icariin-mediated anti-neuroinflammation, as evidenced by the following observations. First, Nrf2 siRNA reversed icariin-reduced microglial activation and pro-inflammatory factors release. Second, a selective inhibitor of HO-1 abolished icariin-mediated anti-neuroinflammatory actions [92]. Tenuigenin is a triterpene compound isolated from *polygala tenuifolia* root. Tenuigenin inhibited LPS-induced inflammatory responses in microglia via activating the Nrf2-mediated HO-1 signaling pathway [93]. Ginsenoside Rg18 was newly identified as a key phytochemical constituent of *Panax ginseng*. Ginsenoside Rg18 suppressed LPS-induced neuroinflammation in BV2 microglia and Aβ-induced oxidative stress in SH-SY5Y neurons via Nrf2/HO-1 induction [94]. Andalucin is a sesquiterpene lactone from *Artemisia lannta*. Andalucin inhibited the LPS-induced release of NO, PGE2, TNF-α, IL-6 and IL-1β. In addition, andalucin reduced the mRNA and protein levels of iNOS and COX-2. Mechanism studies found that andalucin suppressed the neuroinflammation via the promotion of Nrf2-mediated HO-1 levels by blocking the p65-p300 interaction in LPS-activated BV2 microglia [95]. Normally, NO plays a role in neuroprotection and pathophysiological processes by regulating resting

**Table 2.** The category, sources, structure, dose, effects and mechanisms of 16 natural compounds acting on Nrf2/HO-1 pathways

| Natural compound | Category | Sources | Structural formula | Dose | Cell lines | Effects and Mechanisms | Refrence |
|---|---|---|---|---|---|---|---|
| Astragaloside IV | triterpenoid saponin | *Rhododendron brachycarpum* |  | 30, 60 μM | LPS-induced BV2/ primary microglia | ↓ (NO, TNF-α, IL-6); ↑ Nrf2/HO-1 via ERK pathway | [91] |
| Icariin | flavonoid | *Herba Epimedii* |  | 0.01, 0.1 μM | LPS-induced BV2 microglia | ↑ Nrf2/HO-1 pathway | [92] |
| Tenuigenin | triterpene | *polygala tenuifolia* |  | 1, 2, 4 μM | LPS-induced BV2 microglia | ↓ (TNF-α, IL-1β, IL-6, PGE2); ↑ Nrf2/HO-1 pathway | [93] |
| Ginsenoside Rg18 | triterpenoid | *Panax ginseng* |  | 5, 10, 50, 100 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, TNF-α, IL-1β, NO); ↑ Nrf2/HO-1; ↓ Akt/ERK1/2 | [94] |
| Andalucin | sesquiterpene lactone | *Artemisia lannta* |  | 5, 10, 20 μM | LPS-activated BV2 microglia | ↑ Nrf2/HO-1 pathway | [95] |
| Hydrangenol | isocoumarin derivatives | *Hydrangea macrophylla* |  | 5, 10, 20, 40 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, NO); ↓ NF-κB, ↑ Nrf2/HO-1 | [97] |
| Piperine | alkaloids | *Piper nigrum* |  | 25, 50, 100 μM | LPS-stimulated BV2 microglia | ↓ (TNF-α, IL-6, IL-1β, PGE2); ↓ NF-κB, ↑ Nrf2 pathway | [98] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Thymoquinone | benzoquinone | *Nigella sativa* |  | 2.5, 5, 10 μM | LPS-stimulated BV2 microglia | ↓ NF-κB, ↑ Nrf2/ARE | [99] |
| 9-Hydroxy-6,7-dimethoxydalbergiquinol (HDDQ) | chalcone | *Dalbergia odorifera* |  | 5, 10, 20, 40 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, NO, COX-2, PGE2, TNF-α, IL-1β);<br>↓ NF-κB, ↑ HO-1 | [100] |
| CRPE56IGIH | glucoside | *Polygonum multiflorum* |  | 5, 10, 20, 40 μg/mL | LPS-stimulated BV2 microglia | ↓ (NO, PGE2, iNOS, COX-2);<br>↓ NF-κB/MAPK, ↑ Nrf2 | [101] |
| CRPE55IB | glucoside | *Polygonum multiflorum* |  | 5, 10, 20, 40 μg/mL | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, NO, PGE2, TNF-α, IL-6);<br>↑ AMPK/Nrf2 pathways | [103] |
| Emodin | anthraquinone | *Polygonum multiflorum* |  | 5, 10, 20, 40 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, NO, PGE2, TNF-α, IL-6);<br>↑ HO-1 and NQO1 via AMPK/Nrf2 signaling | [104] |
| Glaucocalyxin B | *ent*-kauranoid diterpenoids | *Rabdosia japonica* |  | 2.5, 5, 10 μM | LPS-activated BV2 microglia | ↓ (NO, TNF-α, IL-1β, COX-2, iNOS);<br>↓ NF-κB, p38 MAPK, ↑ HO-1 | [105] |
| Micheliolide | sesquiterpene lactone | *Michelia compressa*, *Michelia champaca* |  | 1, 5, 10 μM | LPS-activated BV2 microglia | ↓ (iNOS, COX-2, NO, TNF-α, IL-6, IL-1β);<br>↓ IκBα/NF-κB, Akt, JNK, p38 MAPK, ERK1/2,<br>↑ Nrf2/HO-1 | [106] |
| Lutein | oxy carotenoid | dark-green leafy vegetables, brightly colored fruit |  | 10, 25, 50 μM | LPS-activated BV2 microglia | ↓ (TNF-α, IL-1β, NO, iNOS, COX-2);<br>↓ JNK, p38MAPK, Akt-stimulated NF-κB,<br>↑ ERK-induced Nrf2 | [107] |
| trans-isoferulic acid | phenolic acid | *Clematis mandshurica* |  | 50, 100, 150 μM | LPS-stimulated BV2 microglia | ↓ (NO, PGE2, iNOS, COX-2);<br>↓ PI3K/Akt-dependent NF-κB, ↑ Nrf2/HO-1 | [108] |

blood flow; however, excessive NO release promotes early blood-brain barrier disruption, as well as causes oxidative injury in microglia [96]. Hydrangenol is an isocoumarin derivative of *Hydrangea macrophylla*. Hydrangenol inhibited LPS-induced NO production in BV2 microglial cells by suppressing the NF-κB pathway and activating the Nrf2-mediated HO-1 pathway [97]. Piperine is the chief alkaloid isolated from *Piper nigrum*. Piperine attenuated LPS-induced inflammatory responses by inhibiting NF-κB activation and activating Nrf2 signaling pathway in BV2 microglia [98]. Thymoquinone is an antioxidant phytochemical that has been shown to inhibit neuroinflammation. Velagapudi's study demonstrated that thymoquinone inhibited LPS-induced neuroinflammation through interference with NF-κB signaling and activation of Nrf2/ARE signaling in BV2 microglia [99]. 9-Hydroxy-6,7-dimethoxydalbergiquinol (HDDQ) is a chalcone compound isolated from *Dalbergia odorifera* T. The inhibitory effect of HDDQ on the NF-κB-related neuroinflammatory response in LPS-stimulated mouse BV2 microglial cells was mediated by HO-1 [100]. CRPE56IGIH is a glucoside isolated from *Polygonum multiflorum* Thunb. CRPE56IGIH displayed anti-neuroinflammatory activity via inhibiting NF-κB/MAPK and upregulating the Nrf2 pathways in LPS-stimulated microglia [101]. Recent studies have reported that AMPK can inhibit the inflammatory response in microglia and macrophages. AMPK activation is also considered a potential therapeutic target for abnormal inflammatory response and oxidative stress [102]. Furthermore, several studies have reported a crosstalk between the AMPK and Nrf2/ARE signaling pathways in immune cells and it is known to be the principal mediator of HO-1 and NQO1 expression. CRPE55IB (sargencuneside) is a glycoside compound isolated from *Polygonum multiflorum* Thunb. CRPE55IB inhibited inflammatory response in LPS-stimulated microglia by upregulating AMPK/Nrf2 pathways [103]. Emodin is an anthraquinone compound extracted from *Polygonum multiflorum*. Emodin decreased the LPS-induced production of NO, PGE2, TNF-α and IL-6 as well as the protein expression of iNOS and COX-2. Emodin exerted anti-neuroinflammatory effects by inducing HO-1 and NQO1 via AMPK/Nrf2 signaling in LPS-stimulated microglia [104]. Glaucocalyxin B is an *ent*-kauranoid diterpenoids isolated from the aerial parts of *Rabdosia japonica*. Glaucocalyxin B decreased the generation of NO, TNF-α, IL-1β, COX-2 and iNOS in the LPS-activated microglia. In addition, glaucocalyxin B inhibited activation of NF-κB, p38 MAPK and generation of ROS in LPS-activated microglia. Furthermore, glaucocalyxin B strongly induced the expression of HO-1 in BV2 microglia cells [105]. Micheliolide is a guaianolide sesquiterpene lactone isolated from *Michelia compressa* and *Michelia champaca*. Micheliolide suppressed LPS-induced neuroinflammatory responses by suppressing the activation of IκBα/NF-κB pathway and Akt pathway. Moreover, micheliolide inhibited LPS-induced the activition of JNK, p38 MAPK, and ERK1/2. Meanwhile, micheliolide markedly promoted antioxidant protein HO-1 expression by enhancing Nrf2 activity [106]. Lutein is an oxy carotenoid that belongs to the xanthophyll family of carotenoids and is found in several dark-green leafy vegetables such as kale and spinach as well as in some brightly colored fruit. Lutein attenuated neuroinflammation in LPS-activated BV2 microglia partly through inhibiting JNK, p38MAPK, and Akt-stimulated NF-κB activation and promoting ERK-induced Nrf2 activation [107]. trans-isoferulic acid is a phenolic acid isolated from the roots of *Clematis mandshurica*. trans-isoferulic acid suppressed NO and PGE2 production in LPS-stimulated BV2 microglial cells via suppression of PI3K/Akt-dependent NF-κB and activation of Nrf2-mediated HO-1 [108].

*Modulatory effects of natural compounds on PI3K/Akt signaling pathway*

*PI3K/Akt signaling pathway:* Phosphatidylinositol 3 kinase (PI3K) generates phosphoinositide-3,4,5- triphosphate (PIP3) in response to a wide range of signals, resulting in the activation of phosphoinositol-dependent protein kinase 1 (PDK1), which translocates to the plasma membrane and activates protein kinase B (PKB/Akt) by phosphorylating its kinase domain at Thr308 and Ser473 residues. Akt is a serine/threonine protein kinase that is constitutively active in cytokine stimulation [109]. PI3K/Akt-dependent signaling pathway has been reported to mediate inflammatory responses, neuronal survival as well as protects against drug-induced damage in neurons via its various downstream targets. PI3K/Akt pathway promotes inflammatory properties in microglia

and is the predominant signaling pathway responsible for the synthesis and production of pro-inflammatory mediators [110]. PI3K/Akt signaling has also been shown to participate in the regulation of gene expression of iNOS and COX-2 in microglia activated by different stimulus including LPS [111]. The activation of PI3K will result in the phosphorylation of its main downstream target, Akt and modulates various transcription factors including NF-κB which further regulate the production of inflammatory factors [112]. So the PI3K-Akt-NF-κB axis is essential for the expression of proinflammatory genes.

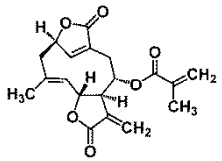
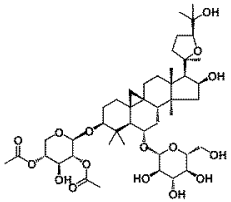
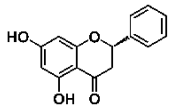
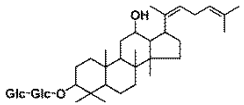
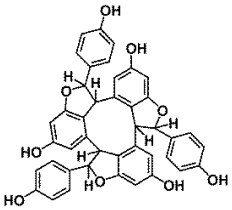
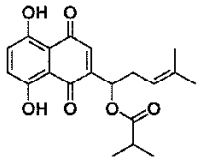
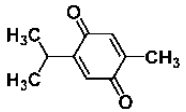
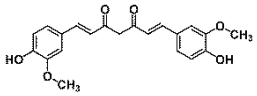
*Natural compounds acting on PI3K/Akt signaling pathway:* The plant-derived natural compounds that exerted anti-neuroinflammatory effect on LPS-activated microglia via inhibition of PI3K/Akt signaling pathways include deoxyelephantopin, isoastragaloside I, pinocembrin, ginsenoside Rg5, α-viniferin, isobutyrylshikonin, thymoquinone and curcumin (**Table 3**).

PI3K/Akt and MAPKs have been considered as two major signaling pathways that attenuate the translocation of NF-κB in neuroinflammation. Deoxyelephantopin is a major sesquiterpene lactone isolated from *Elephantopus scaber*. Deoxyelephantopin modulated neuroinflammatory response through MAPKs and PI3K/Akt-dependent NF-κB signaling pathways in LPS-stimulated BV2 microglial cells. The enhancement of anti-inflammatory cytokines, IL-4 and IL-10 concomitantly with the reduction of pro-inflammatory cytokines (Interferon-γ, IL-1β, IL-2, IL-6, IL-12 and TNF-α), chemokines (CCL21 and CCL5/RANTES) and galectin-3 were found upon deoxyelephantopin treatment [113]. Isoastragaloside I is a natural saponin molecule found within the roots of *Astragalus membranaceus*. Isoastragaloside I dose-dependently inhibited the excessive release of NO and TNF-α in the LPS-stimulated BV2 cells. Moreover, it decreased the production of iNOS and COX-2, and mitigated the gene expression of IL-1β, TNF-α and iNOS induced by LPS. Isoastragaloside I prevented LPS-induced microglial activation probably by inhibiting the activation of the NF-κB via PI3K/Akt and MAPK signaling pathways [114]. Pinocembrin is one of the primary flavonoids from *Pinus* heartwood and *Eucalyptus*. Pinocembrin inhibited LPS-induced inflammatory mediators (TNF-α, IL-1β, NO, PGE2) production and LPS-induced iNOS and COX-2 expression by suppressing PI3K/Akt/NF-κB signaling pathway. Furthermore, pinocembrin induced nuclear translocation of Nrf2 and expression of HO-1 [115]. Ginsenoside Rg5 is one of the main constituents of steamed ginseng and belongs to protopanaxadiol ginsenosides. Ginsenoside Rg5 suppressed LPS-induced NO production and proinflammatory TNF-α secretion. In addition, ginsenoside Rg5 inhibited the mRNA expressions of iNOS, TNF-α, IL-1β, COX-2 and MMP-9 induced by LPS. Further mechanistic studies revealed that ginsenoside Rg5 inhibited the phophorylations of PI3K/Akt and MAPKs and the DNA binding activities of NF-κB and AP-1, which were upstream molecules controlling inflammatory reactions. Moreover, ginsenoside Rg5 suppressed ROS production with upregulation of HO-1 expression in LPS-stimulated BV2 cells [116]. α-Viniferin, an oligostilbene of trimeric resveratrol, was isolated for the first time from *Caragana chamlagu.* The study indicated that α-viniferin suppressed the expression of proinflammatory genes iNOS and COX-2 in the early stage of inflammation by inhibiting the Akt/PI3K-dependent NF-κB activation and inhibited the production of proinflammatory mediators NO and PGE2 in the late stage by stimulating Nrf2-mediated HO-1 signaling pathway in LPS-stimulated BV2 microglial cells [117]. Isobutyrylshikonin is a naphthoquinone compound isolated from *Lithospermum erythrorhizon.* The study suggested that isobutyrylshikonin inhibited LPS-induced NO and PGE2 production in BV2 microglial cells by suppressing the PI3K/Akt-mediated NF-κB pathway [118]. Similarly, Wang's study demonstrated that thymoquinone inhibited LPS-induced inflammatory mediators production in BV2 microglial cells by suppressing PI3K/Akt/NF-κB signaling pathway [119]. Curcumin is a phenolic natural product isolated from the rhizome of *Curcuma longa*. Curcumin played an important role in the attenuation of LPS-induced inflammatory responses in microglial cells and that the mechanisms involved down-regulation of the PI3K/Akt signaling [120].

*Modulatory effects of natural compounds on JAK/STAT signaling pathway*

*JAK/STAT signaling pathway:* Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling plays an essential role in

**Table 3.** The category, sources, structure, dose, effects and mechanisms of 8 natural compounds acting on PI3K/Akt pathways

| Natural compound | Category | Sources | Structural formula | Dose | Cell lines | Effects and Mechanisms | Refrence |
|---|---|---|---|---|---|---|---|
| Deoxyelephantopin | sesquiterpene lactone | *Elephantopus scaber* |  | 0.1, 0.25, 0.5 μM | LPS-stimulated BV2 microglia | ↑ (IL-4, IL-10),<br>↓ (IFN-γ, IL-1β, IL-2, IL-6, IL-12, TNF-α, CCL21, CCL5/RANTES, galectin-3);<br>↓ MAPKs, PI3K/Akt/NF-κB | [113] |
| Isoastragaloside I | saponin | *Astragalus membranaceus* |  | 25, 50, 100 μM | LPS-stimulated BV2 microglia | ↓ (NO, TNF-α, IL-1β, iNOS, COX-2);<br>↓ NF-κB, PI3K/Akt, MAPK pathways | [114] |
| Pinocembrin | flavonoid | *Pinus heartwood*, *Eucalyptus* |  | 50, 100, 200 μg/mL | LPS-stimulated BV2 microglia | ↓ (TNF-α, IL-1β, NO, PGE2, iNOS, COX-2);<br>↓ PI3K/Akt/NF-κB,<br>↑ Nrf2/HO-1 signaling | [115] |
| Ginsenoside Rg5 | triterpenoid saponin | steamed ginseng |  | 10, 30, 50 μM | LPS-stimulated BV2 microglia | ↓ (iNOS, COX-2, MMP-9, NO,TNF-α, IL-1β, ROS);<br>↓ PI3K/Akt, MAPKs, NF-κB, AP-1;<br>↑ HO-1 | [116] |
| α-Viniferin | oligostilbene of trimeric resveratrol | *Caragana chamlagu* |  | 1, 3, 5 μM | LPS-stimulated BV2 microglia | ↓ Akt/PI3K/NF-κB,<br>↑ Nrf2/HO-1 pathway | [117] |
| Isobutyrylshikonin | naphthoquinone | *Lithospermum erythrorhizon* |  | 0.25, 0.5, 1 μM | LPS-stimulated BV2 microglia | ↓ (NO, PGE2, iNOS, COX-2);<br>↓ PI3K/Akt/NF-κB pathway | [118] |
| Thymoquinone | benzoquinone | *Nigella sativa* |  | 3, 6, 12 μM | LPS-stimulated BV2 microglia | ↓ (TNF-α, IL-1β, NO, PGE2);<br>↓ PI3K/Akt/NF-κB pathway | [119] |
| Curcumin | phenolic | *Curcuma longa* |  | 10, 30, 40, 50 μM | LPS-induced BV2 microglia | ↓ (iNOS, NO, proinflammatory cytokines);<br>↓ PI3K/Akt signaling | [120] |

promoting and modulating immune and inflammatory processes [121]. Different expression of the JAK/STAT pathway have been associated with pathological CNS conditions such as cerebral ischemia, traumatic brain injury and brain inflammation [122]. JAK2 belongs to the JAK family and the major substrate for JAK2 is the family of STATs, including STAT1 and STAT3. JAK2 transduces the LPS-induced signals to downstream molecules to activate the phosphorylation and nuclear translocation of STAT1/3, leading to the expression of proinflammatory genes [123], resulting in the excessive accumulation of the corresponding inflammatory mediators. Thus the inhibition of JAK2/STAT3 pathway may provide a therapeutic approach for neuroinflammatory injuries.

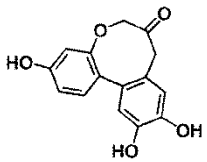
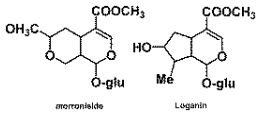
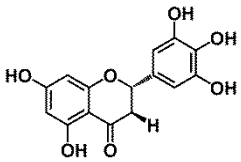
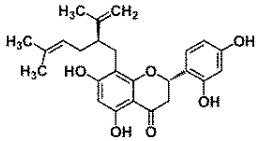
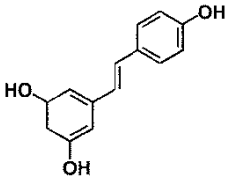
*Natural compounds acting on JAK/STAT signaling pathway:* The plant-derived natural compounds that exerted anti-neuroinflammatory effect on LPS-activated microglia via inhibition of JAK/STAT signaling pathways include protosappanin A, cornel iridoid glycoside, ampelopsin, sophoraflavanone G and resveratrol (**Table 4**).

Protosappanin A is a major biphenyl compound isolated from *Caesalpinia sappan*. Protosappanin A significantly inhibited the production of TNF-α and IL-1β in LPS-activated BV2 microglia. Moreover, the mRNA expressions of IL-6, IL-1β, and MCP-1 were reduced by protosappanin A in a dose-dependent manner. Furthermore, protosappanin A suppressed JAK2/STAT3-dependent inflammation pathway through down-regulating the phosphorylation of JAK2 and STAT3, as well as STAT3 nuclear translocation against LPS treatment [124]. Cornel iridoid glycoside is the main component extracted from *Cornus officinalis*. Cornel iridoid glycoside exerted therapeutic potential by modulating microglia polarization and reducing the expression and release of proinflammatory cytokines, chemokines and inhibiting phosphorylation in the JAK/STAT cell signaling pathway [125]. Ampelopsin is a type of flavanonol derivative from *Ampelopsis grossedentata*. Ampelopsin attenuated LPS-induced inflammatory response through the inhibition of the NF-κB and JAK2/STAT3 signaling pathways in microglia [126]. Sophoraflavanone G is a major flavonoid found in the *Sophora alopecuroides*. Sophoraflavanone G displayed anti-neuroinflammatory activity in LPS-activated BV2 microglia. Sophoraflavanone G inhibited the neuroinflammation by MAPKs, PI3K/Akt, JAK/STAT and Nrf2/HO-1 signaling pathways [127]. Peroxisome proliferator-activated receptor co-activator-1α (PGC-1α) is a transcription co-activator for nuclear receptors and plays key integrator roles in the transcriptional control of cellular energy metabolism, oxidative stress defense, mitochondrial function and biogenesis [128]. Resveratrol is a natural polyphenol enriched in the skin of grapes, blueberries, peanuts, raspberries, mulberries and red wine. Yang's study demonstrated that resveratrol reduced inflammatory damage and promoted microglia polarization to the M2 phenotype via PGC-1α in LPS-induced neuroinflammation. PGC-1α not only suppressed LPS-evoked M1 marker expression by inhibition of NF-κB activity but also increased M2 marker expression by coactivation of the STAT6 and STAT3 pathways [129].

## Conclusions and future prospects

In the nervous system, neurodegenerative diseases are multifactorial debilitating disorders that are characterized by progressive dysfunction and neuronal injury leading to a slow but irreversible deterioration of brain functions which affects around 30 million individuals worldwide [130]. Neuroinflammation is strictly associated with the pathogenesis of neurodegenerative diseases and its main feature is considered the microglia activation in CNS. Differential activation of microglia constitutes a central point of regulation in neuroinflammation, which can yield neurotoxic or neurosupportive environments, being critical for neurons' fate. Therefore, normalization of microglia activation is considered a promising strategy for developing drugs that can treat or prevent inflammation-related brain diseases. In recent years, an increasing number of researchers have attempted to search for efficient neuroprotective agents using natural compounds of plant origin. These natural compounds are often well known and have been used for centuries in traditional medicine and now are rediscovered by scientists and studied in detail in order to understand their molecular mechanisms of action. They possess neuroprotective potential probably related to their ability to influence and modulate the inflammatory re-

**Table 4.** The category, sources, structure, dose, effects and mechanisms of 5 natural compounds acting on JAK/STAT pathways

| Natural compound | Category | Sources | Structural formula | Dose | Cell lines | Effects and Mechanisms | Refrence |
|---|---|---|---|---|---|---|---|
| Protosappanin A | biphenyl | *Caesalpinia sappan*. |  | 12.5, 25, 50 mM | LPS-induced BV2 microglia | ↓ (TNF-α, IL-1β, IL-6, IL-1β, MCP-1);<br>↓ JAK2-STAT3 pathway | [124] |
| Cornel iridoid glycoside | glycoside | *Cornus officinalis* |  | 25, 50, 100, 200 μg/mL | LPS/IFN-γ-stimulated BV2 microglia | ↓ (proinflammatory cytokines, chemokines);<br>modulate microglia polarization;<br>↓ JAK/STAT signaling | [125] |
| Ampelopsin | flavanonol derivative | *Ampelopsis grossedentata* |  | 10, 30, 50 μM | LPS-induced BV2/primary microglia | ↓ (NO, PGE2, iNOS, COX-2, IL-1β, IL-6, TNF-α);<br>↓ NF-κB and JAK2/STAT3 pathways | [126] |
| Sophoraflavanone G | flavonoid | *Sophora alopecuroides* |  | 5, 10, 20 μM | LPS-activated BV2 microglia | ↓ (NO, PGE2, iNOS, COX-2, IL-1β, IL-6, TNF-α);<br>↓ MAPKs, PI3K/Akt, JAK/STAT,<br>↑ Nrf2/HO-1 pathways | [127] |
| Resveratrol | polyphenol | grapes, blueberries, peanuts, raspberries, mulberries, red wine |  | 5, 10, 20, 50 μM | LPS-induced BV2 microglia | reduce inflammatory damage and promote microglia polarization via PGC-1α;<br>↓ NF-κB, ↑ STAT6, STAT3 pathways | [129] |

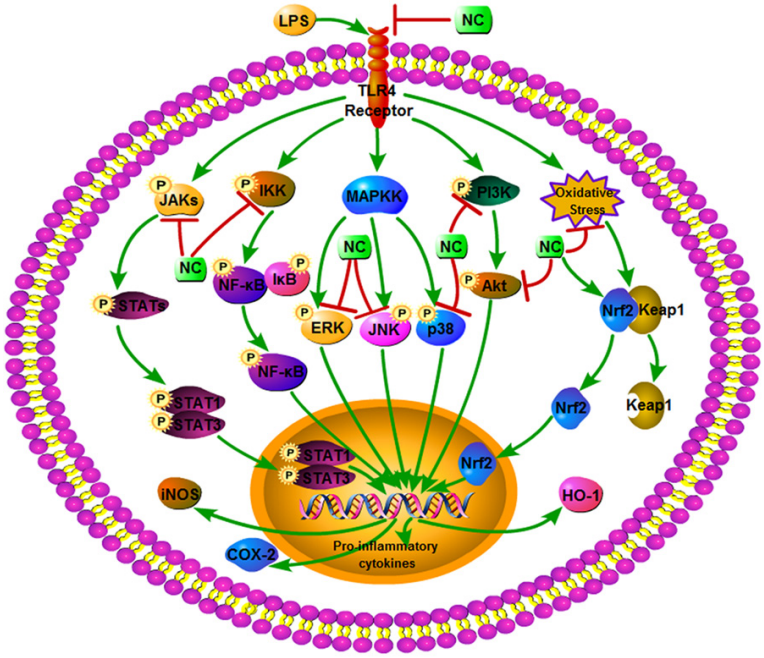



**Figure 2.** Proposed signaling mechanism for the effects of natural compounds on LPS-induced neuroinflammation in BV2 microglia.

sponses involved in neurodegeneration. In this review, we summarized the detailed research progress on the natural compounds derived from medical plants with potential anti-neuroinflammatory effects and their molecular mechanisms on modulating the microglia function. The natural compounds that efficacious in inhibiting the microglia activation include flavonoids, glycosides, phenolics, terpenoids, quinones, alkaloids, lignans, coumarins, chalcone, stilbene and others (biphenyl, phenylpropanoid, oxy carotenoid). They can reduce the expression of neurotoxic mediators (NO, PGE2, iNOS, COX-2) and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), down-regulate inflammatory markers and prevent neural damage. They exert anti-neuroinflammatory effects by modulating relevant signaling pathways (NF-κB, MAPKs, Nrf2/HO-1, PI3K/Akt, JAK/STAT) as demonstrated by experimental data (**Figure 2**). The present work reviews the role of microglia activation in neuroinflammation, highlighting the potential anti-inflammatory effects of natural compounds as a promising approach to develop innovative neuroprotective strategy. Nowadays, tremendous new findings have further advanced the inflammatory mechanism associated with neurodegeneration. And the development of natural compounds with anti-neuroinflammatory effects is of great value for the prevention or treatment of nervous system diseases and for neuronal regenerative medicine. With more and more attention focused on the disease-modifying natural products, the neuroprotective effects of medicinal plant-derived natural compounds have become increasingly prominent. It is desirable to make more brilliant advances on neuroprotective natural compounds, which would create a new alternative for prevention and treatment neurobiological disorders.

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## Disclosure of conflict of interest

None.

## Abbreviations

CNS, Central nervous system; BBB, Blood-brain barrier; AD, Alzheimer's disease; PD, Parkinson's disease; MS, Multiple sclerosis; HD, Huntington's disease; ALS, Amyotrophic lateral sclerosis; NO, Nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; TNF-α, Tumour necrosis factor α; IL-6, Interleukin-6; IL-1β, Interleukin-1β; PGE2, Prostaglandin E2; LPS, Lipopolysaccharides; TLR4, Toll like receptor 4; PRR, Pattern recognition receptor; MyD88, Myeloid differentiation factor 88; TRIF, Toll/IL-1 receptor domain-containing adapter induction of the interferon-β; NF-κB, Nuclear factor-kappa B; IκB, Inhibitors of κB; IKK, IκB kinase; TAK1, TGF-β activated kinase 1; MAPKs, Mitogen-activated protein kinases; ROS, Reactive oxygen species; IFN-γ, Interferon-γ; TRAF6, TNF-receptor-associated factor 6; AR, Aldose reductase; PLC, Phospholipase C; PKC, Protein kinase C; JNKs, c-Jun

N-terminal kinases; ERK, Extracellular signal-regulated kinases; IRF3, Interferon regulatory factor 3; mTOR, Mammalian target of rapamycin; IRAK-4, Interleukin-1 receptor-associated kinase 4; TAB2, TAK1-binding protein 2; JAK, Janus kinase; STAT, Signal transducers and activators of transcription; Nrf2, Nuclear factor erythroid 2 related factor 2; ARE, Antioxidant response elements; NQO1, NADPH quinone acceptor oxidoreductase 1; HO-1, Heme oxygenase-1; AMPK, AMP-activated protein kinase; PI3K, Phosphatidylinositol 3 kinase; Akt/PKB, Protein kinase B; PIP3, Phosphoinositide-3,4,5-triphosphate; PDK1, Phosphoinositol-dependent protein kinase 1.

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