# Inflammatory signaling pathways in the treatment of Alzheimer's disease with inhibitors, natural products and metabolites (Review)

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**Abstract.** The intricate nature of Alzheimer's disease (AD) pathogenesis poses a persistent obstacle to drug development. In recent times, neuroinflammation has emerged as a crucial pathogenic mechanism of AD, and the targeting of inflammation has become a viable approach for the prevention and management of AD. The present study conducted a comprehensive review of the literature between October 2012 and October 2022, identifying a total of 96 references, encompassing 91 distinct pharmaceuticals that have been investigated for their potential impact on AD by inhibiting neuroinflammation. Research has shown that pharmaceuticals have the potential to ameliorate AD by reducing neuroinflammation mainly through regulating inflammatory signaling pathways such as NF-κB, MAPK, NLRP3, PPARs, STAT3, CREB, PI3K/Akt, Nrf2 and their respective signaling pathways. Among them, tanshinone IIA has been extensively studied for its anti-inflammatory effects, which have shown significant pharmacological properties and can be applied clinically. Thus, it may hold promise as an effective drug for the treatment of AD. The present review elucidated the inflammatory signaling pathways of pharmaceuticals that have been investigated for their therapeutic efficacy in AD and elucidates their underlying mechanisms. This underscores the auspicious potential of pharmaceuticals in ameliorating AD by impeding neuroinflammation.

**Contents**



## 1. Introduction

AD is a common neurodegenerative disorder characterized by gradual cognitive decline, memory loss, and behavioral

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*Abbreviations:* AD, Alzheimer's disease; Aβ, amyloid β; APP/PS1, amyloid-β protein/presenilin-1; 5XFAD, 5X familial Alzheimer's disease; p-, phosphorylated; AChE, acetylcholinesterase; APN, Adiponectin; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; ASC, apoptosis-associated speck-like protein; BBB, blood-brain barrier; BACE1, β-site amyloid precursor protein cleaving enzyme 1; NF-κB, nuclear factor-kappa-B; CNS, central nervous system; COX-2, cyclooxygenase-2; CHI3L1, chitinase-3 like-protein-1; CREB, cyclic AMP response element binding; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; Iba-1, ionized calcium binding adaptor molecule 1; GSK-3β, glycogen synthase kinase-3β; STAT3, signal transducers and activators of transcription 3; GSDMD, gasdermin D; HCK, Hematopoietic cell kinase; HO-1, Haem oxygenase-1; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; AP-1, activator protein 1; JNK, c-Jun NH2-terminal kinases; JAK2, Janus kinase 2; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; MAPK, mitogen-activated protein kinase; MK2, MAPK-activated protein kinase II; MEK, mitogen-activated extracellular signal-regulated kinase; PGE2, prostaglandin E2; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; Nrf2, nuclear kinase II; MEK, mitogen-activated extracellular signal-regulated kinase; PGE2, prostaglandin E2; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PINK1, PTEN-induced kinase 1; PPARs, peroxisome proliferator-activated receptors; PTEN, phosphate and tensin homolog deleted on chromosome 10; PKA, protein kinase A; PKG, cGMP-dependent protein kinase; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; ROCK, Rho-dependent coiled-coil kinase; SOCS, suppressor of cytokine signaling; TLRs, Toll-like receptors; WDFY1, WD repeat and FYVE domain-containing 1

*Key words:* Alzheimer's disease, neuroinflammation, inhibitor, inflammatory signaling pathways, treatment

changes (1). AD is mainly characterized by the accumulation of extracellular amyloid β (Aβ), which forms senile plaques, and intracellular hyperphosphorylated tau, which binds to microtubules and leads to the development of neurofibrillary tangles (2). The disease is becoming increasingly prevalent, with projections estimating a global population of 115 million patients with AD by 2050 (3). With a growing aging population, the management of AD is becoming increasingly critical.

The pathogenesis of AD is multifactorial and involves a number of hypotheses, including the cholinergic theory, the amyloid cascade theory, the oxidative stress theory, the tau protein hypothesis and the neuroinflammation hypothesis (4). Evidence supports the neuroinflammation as a crucial factor in the development of AD (5,6). Neuroinflammation (7-9) is present in the majority of patients with AD (10) and animal models (11), particularly in the cerebral cortex and hippocampus (12,13). Elevated levels of inflammatory factors and increased activation of microglia around senile plaques observed in patients with AD further support this hypothesis (14). In addition, whole-genome studies of post-mortem brain samples from patients with AD have shown upregulation of inflammation-related genes and significant downregulation of anti-inflammatory molecules (15). Activated microglia, responding to Aβ (16), demonstrate a significant inflammatory response highly correlated with the severity of AD (17). Taken together, these findings suggest that neuroinflammatory responses mediated by microglial cell activation may play a central role in the pathogenesis of AD.

Under normal circumstances, highly active microglia cells efficiently monitor the entire brain in real time (18), detecting abnormalities such as pathogens and cellular debris (19,20) and providing essential support to maintain optimal brain function (21). However, when the brain is exposed to abnormal conditions, microglia become activated and switch to a transforming state, migrating towards the site of injury to remove pathogens, cellular debris and degenerated cells (22). Depending on their activation state and environmental stimuli, microglia cells can be classified as either the pro-inflammatory M1 type or the anti-inflammatory M2 type (23). In the early stages of AD, microglia play a crucial role in maintaining a dynamic balance of amyloid protein in the brain by engulfing and clearing excess Aβ, thereby helping to delay disease progression. However, as the disease progresses, excessive accumulation of Aβ can lead to overactivation of microglia cells, causing them to adopt a pro-inflammatory M1 type (24). In the central nervous system (CNS), activated microglia are the primary source of inflammatory molecules, such as cytokines, chemokines, neurotransmitters, reactive oxygen species (ROS) and nitric oxide (NO) (25). Inflammatory molecules trigger a positive feedback mechanism that activates more microglia and thus further exacerbating the neuroinflammatory response (25,26). As a result, secreted inflammatory mediators facilitate the migration of monocytes and lymphocytes to the site of inflammation, where they penetrate the blood-brain barrier (BBB), exacerbating CNS inflammation and leading to sustained neuronal damage (27), ultimately culminating in cognitive decline. Several inhibitors, drugs and their active ingredients can exert an anti-neuroinflammatory effects, with different drugs acting via single or multiple signaling pathways. Therefore, it is essential to consolidate research findings to identify potential drug candidates for the prevention and treatment of AD.

Neuroinflammation is a critical factor and even a core event in the pathogenesis of AD (17,28). Microglia, as the primary immune cells in brain tissue, play an essential role in neuroinflammation through multiple targets and signaling pathways. Therefore, the development of drugs or inhibitors that target microglia could alleviate neuroinflammation, which could have a positive effect on both the prevention and treatment of AD. The present study conducted a literature search using keywords the 'inhibitors', 'microglia', 'inflammation' and 'Alzheimer's disease' in PubMed between 2012 and 2022 to comprehensively review the major signaling pathways involved in microglia activation and the ways in which drugs exert anti-neuroinflammatory effects by targeting these pathways. Out of the 327 articles retrieved, 35 were excluded, including reviews, commentaries, retractions, or unavailability online. Also excluded were 201 articles that did not involve signaling pathways. Finally, 96 references were included. In addition, 'medicine' and 'drugs' were added as keywords to the search to further identify promising drug candidates for AD prevention.

## 2. NF-κB and MAPK signaling pathways

*NF-κB (nuclear factor-kappa-B).* The NF-κB signaling pathway is a complex protein interaction network (29) that plays a critical role in regulating gene expression in response to various stimuli, including pro-inflammatory signals (30). In most cell types, NF-κB is activated by the classical pathway, which involves a dimer composed of p50 and p65 subunits (31). In the inactive state, the NF-κB/IκB dimer is inhibited by IκB and remains sequestered in the cytoplasm (32,33). Upon activation of the NF-κB/IκB dimer by pro-inflammatory signals, IκB kinase (IKK) phosphorylates IκB, leading to its degradation. This allows NF-κB to dissociate from the complex, enter the nucleus, and activate the transcription of cytokines and adhesion molecules (34-36), contributing to the pathogenesis of neuroinflammatory diseases such as AD.

NF-κB is widely expressed in brain tissue and plays a critical regulatory role in various target genes within the CNS. Its regulatory scope encompasses oxidative stress, neuroinflammation and microglia activation (31). In particular, excessive activation of NF-κB has been implicated in the neuropathological features of AD. Multiple studies have identified increased activation of NF-κB in the brains of patients with AD (31,37), particularly in the most affected brain regions (38-40). Additionally, the activation of NF-κB by Aβ leads to further production of Aβ, exacerbating the pathology of AD (41,42). Moreover, NF-κB not only acts downstream of tau but also seems to directly mediate its cognitive toxicity (43). This increased DNA-binding activity of NF-κB leads to aggravated oxidative stress, which exacerbates neurotoxicity. In addition, downstream pro-inflammatory mediators are activated, thereby affecting neuronal function (44,45). Above all, activation of glial cells via the NF-κB pathway serves as a critical link in the neuroinflammatory response (46), further amplifying neuroinflammation and worsening AD pathology (47,48). As such, modulation of the NF-κB signaling pathway in microglia

may represent a promising new approach to the prevention and treatment of AD.

Studies have shown that certain compounds found in traditional Chinese herbal medicine possess the capacity to inhibit NF-κB activation and exert anti-inflammatory effects. Rutin, a natural flavonoid glycoside with anti-inflammatory and antioxidant properties (49), is a promising neuroprotective agent for neurodegenerative diseases (50). A recent study has revealed that treatment with Rutin can reduce NF-κB activation in the Tau-P301S mouse, resulting in lower levels of IL-1 and TNF-α in brain tissue, thereby counteracting neuroinflammation (51). Results consistent with *in vivo* findings were also observed in microglia induced with tau oligomers (51). Similarly, piperlongumine, an alkaloid amide from *Piper longum*, was found to be neuroprotective effects (52) against lipopolysaccharide (LPS)-induced neuroinflammation by inhibiting the NF-κB pathway and reducing the expression of key pro-inflammatory mediators such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, and IL-6. Thus, these compounds show therapeutic potential for the treatment of neuroinflammatory disorders by modulating the NF-κB signaling pathway in microglia (53). Bee venom, which contains various peptides, enzymes, and biogenic amines, has been shown to be effective in the treatment of diseases such as arthritis, rheumatism and cancer (54). A study has highlighted its potential for treating AD by inhibiting the expression of neuroinflammatory proteins such as β-site amyloid precursor protein cleaving enzyme 1 (BACE1), COX-2, iNOS, glial fibrillary acidic protein (GFAP), and ionized calcium binding adaptor molecule 1, *in vitro* and *in vivo*, through inactivation of the NF-κB pathway, resulting in a reduction in LPS-induced memory impairment (55). Punicalagin, a polyphenol sourced from pomegranate fruit, has antioxidant, anti-proliferative and anti-inflammatory properties (56). It has been shown to bind directly to NF-κB, impede IκB degradation and prevent the nuclear translocation of p50 and p65, thereby inhibiting the production of ROS, NO, TNF-α and IL-1β in LPS-induced BV-2 microglia (57). Similarly, tenuifolin, a valuable neuroprotective compound extracted from *Polygala tenuifolia* Willd, can block the activation of the NF-κB pathway and subsequently improve cognitive impairment symptoms in AD (58). Piperine, a crystalline alkaloid extracted from pepper, has several properties such as anticarcinogenic, stimulatory, anti-inflammatory and antiulcer activities (59). Furthermore, piperine derivatives, such as (2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)-N-[4-(hydroxymethyl) phenyl] penta-2,4-dienamide (D4) have demonstrated anti-neuroinflammatory effects (60) by inhibiting the translocation of NF-κB and suppressing the expression of iNOS and the secretion of NO, TNF-α, and IL-1β in LPS-induced human microglia clone 3. In addition, an *in silico* study showed excellent D4 bioavailability after oral administration (61). *Bupleurum falcatum* L. (BF) is a traditional oriental medicine commonly used in the treatment of chronic hepatitis and autoimmune diseases (62). It has been demonstrated that the ethanol extract of BF (BFE) can inhibit the expression of pro-inflammatory genes and NF-κB p65/RELA mRNA in BV2 microglia that have been activated with LPS. This suggests that NF-κB is a molecular target of BFE (63). In addition, BFE has been shown to inhibit the activation of microglia in the hippocampus and substantia nigra of LPS-treated mice (63), suggesting its potential as a treatment for AD. Similarly, macasiamenene F (MF), a compound extracted from *Macaranga siamensis* S. J. Davies (Euphorbiaceae), has also been shown to have promising potential in the treatment of neuroinflammatory responses. MF treatment significantly suppresses NF-κB activity and TNF-α expression in LPS-induced human monocytes (64), and similar responses may occur in microglia of brain given their phenotypic similarity. Miconazole (MCZ) is an azole drug commonly used as an antifungal agent that can cross the BBB and exhibits neuroprotective effects (64,65). MCZ can reduce the expression of ionized calcium binding adaptor molecule 1 (Iba-1) reactive cells and downregulate the expression of GFAP, Iba-1, and COX-2 in the hippocampus by inhibiting the NF-κB signaling pathway in a mouse model of $A\beta_{1-42}$-induced memory impairment. This anti-inflammatory effect of MCZ was further confirmed in an LPS-induced BV2 microglia model (66).

Several drugs have been developed to target specific components of the body and exert anti-neuroinflammatory effects by inhibiting NF-κB (67-70). Among these, LD55, a resveratrol analogue, is widely used as a novel inhibitor of NF-κB activation (71). A study has shown that dietary supplementation with LD55 can effectively suppress the activation of microglia in transgenic amyloid-β protein/presenilin-1 (APP/PS1) mice, diminish the density of Aβ plaques in the brain and notably reduce them by 2-15 times in the hippocampal region. These findings suggest that LD55 may provide some relief from the burden of Aβ plaques and neuroinflammation in AD models (67). Additionally, glucocorticoid-induced leucine zipper (GILZ), which functions as a transcriptional regulatory protein, has the ability to impede the activity of NF-κB (72,73). A small molecule GILZ analogue, GA, was found to inhibit the levels of NF-κB p65 in the brains of 5XFAD (familial Alzheimer's disease) mice. Furthermore, GA can downregulate the expression of inflammatory factors while hindering the proliferation and activation of hippocampal microglia (68). Consequently, this leads to the suppression of neuroinflammation. Chitinase-3 like-protein-1 (CHI3L1) is a secreted, inflammatory glycoprotein that is expressed in a number of chronic neuroinflammatory diseases including AD, making it a potential biomarker for AD diagnosis (74). Conversely, CHI3L1 deficiency has been shown to attenuate microglia-mediated inflammation and inhibit the progression of AD (75,76). Study has shown that the CHI3L1 inhibitor, K284-6111, can suppress NF-κB activation and the expression of related inflammatory factors in AD animal models following intracerebroventricular infusion of $A\beta_{1-42}$ and in LPS-induced BV-2 microglia cells (69). Furthermore, the anti-neuroinflammatory effects of K284-6111 are also observed in a Tg2576 mouse model and in Aβ-induced BV2 microglia, implicating the extracellular signal-regulated kinases (ERK)-mediated pentraxin 3 and NF-κB pathways (16). DL0410, an acetylcholinesterase (AChE) inhibitor, has been shown to suppress the receptor for advanced glycation end products (RAGE)/NF-κB signaling pathway, resulting in inhibition of D-galactose-induced microglia activation. This results in the downregulation of COX2 and iNOS expression, ultimately suppressing inflammation in the cortex and hippocampus of the brain (70).

Toll-like receptors (TLRs) are essential pattern recognition receptors in the immune and inflammatory responses, with TLR4 being highly expressed on microglia (77). However, excessive activation of TLRs can initiate a cascade of events, leading to activation of NF-κB in the brain, resulting in the synthesis and release of various inflammatory mediators that contribute to neuronal damage (78,79). Therefore, targeting the TLR/NF-κB pathway may prove beneficial in the treatment of AD. Several studies have illustrated that natural compounds can reduce neuroinflammation by inhibiting the TLR4/NF-κB pathway (80-82). One such compound is epigallocatechin-3-gallate (EGCG), a polyphenol found in green tea that has been extensively studied for its neuroprotective effects (83). EGCG is known to suppress the activation of both classical NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasomes and caspase-11-mediated non-classical inflammasomes via the TLR4/NF-κB pathway, thereby effectively exerting its anti-inflammatory properties (80). Genistein (Gen), a compound derived from Soybean isoflavone (SIF) (84), has been shown to improve memory abilities in patients with AD and to attenuate inflammation in $A\beta_{25-35}$-induced BV-2 microglia through inhibition of the TLR4/NF-κB signaling pathway. These findings suggest that a diet rich in plant-derived Gen may be beneficial in reducing the risk of AD by alleviating inflammation (81). In addition, oxysophoridine extracted from *Sophora alopecuroides* L. seeds (85,86) was found to downregulate the expression of TNF-α and IL-1β in Aβ-induced BV-2 cells, with therapeutic effects comparable to those of the TLR4 inhibitor TAK-242. These results demonstrate the promising anti-neuroinflammatory properties of oxysophoridine (82). The initial interaction between CD14 and TLR4 is a crucial step in the activation of neuroinflammatory signals induced by LPS (87). A study has identified a novel biphenyl compound, called Protosappanin A (PTA), derived from *Caesalpinia sappan* L., which effectively inhibits neuroinflammation *in vitro* (88). PTA achieves this by disrupting the CD14-TLR4 interaction in BV-2 microglia that are stimulated by LPS, thereby inhibiting the NF-κB signaling pathway (88). Similarly, resveratrol, a natural neuroprotectant agent, has been shown to significantly reduce microglia-mediated neuroinflammation (89). Oral administration of resveratrol to APP/PS1 mice significantly reduced the number of activated microglia around amyloid plaques (90). Further *in vitro* research revealed that resveratrol's mechanism of action involves disruption of TLR4 oligomerization to attenuate the TLR4/NF-κB/STAT signaling pathway, ultimately leading to a reduction in TNF-α and IL-6 production (90).

Upon activation, TLR4 recruits the adaptor myeloid differentiation factor 88 (MyD88), which initiates downstream activation of the transcription factor NF-κB (91). Certain active compounds in some traditional Chinese medicines have been found to interfere with this pathway and exert anti-neuroinflammatory effects. For example, Icariside II (ICS II), an active component of *Epimedium*, has been shown to have multiple pharmacological activities, including anti-inflammatory, anticancer and anti-aging (92,93). In an LPS-induced SD rat model of neuroinflammation, ICS II demonstrated potent anti-inflammatory effects by reducing the expression of the microglia marker Iba-1 and downregulating related pro-inflammatory cytokine proteins by intervening in the TLR4/MyD88/NF-κB pathway (94). Similarly, DL0410 is a dual inhibitor of both AChE and butyrylcholinesterase with a unique structural scaffold (95). This compound has been shown to improve memory when administered with $A\beta_{1-42}$ and scopolamine administration (96), as well as cognitive impairment when administered with D-galactose. It holds significant potential as a therapeutic agent for AD by inhibiting the TLR4-mediated/MyD88/NF-κB signaling pathway and reducing pro-inflammatory cytokines (such as TNF, IL-1 and IL-6), while increasing the anti-inflammatory cytokine IL-10 to combat neuroinflammation (97). ATP50-3 is a purified product that is extracted from crude polysaccharides obtained from the traditional Chinese medicine *Acorus tatarinowii* (98,99). *In vitro* study has shown that it effectively inhibits the activation of NF-κB and the expression of TLR4, MyD88, phosphorylated (p)-PI3K (phosphoinositide 3-kinase), p-Akt (p-, phosphorylated), and inflammatory mediators in LPS-induced BV2 cells (100). Moreover, its anti-inflammatory efficacy is further enhanced by the TLR4 inhibitor TAK242 and the PI3K inhibitor LY294002, suggesting that its neuroprotective effects against neuroinflammation are due to the regulation of the TLR4/MyD88/NF-κB and PI3K/Akt signaling pathways (100). Another natural compound, dihydromyricetin (DHM) from *Ampelopsis grossedentata*, has also been found to exhibit promising anti-inflammatory effects (101) and is being considered as a potential treatment for AD. In an LPS-induced inflammation model of BV-2 microglia, DHM was found to downregulate pro-inflammatory cytokine mRNA expression by inhibiting TLR4 and MyD88 expression, and activation of the NF-κB pathway induced by LPS (102). These results strongly suggest that DHM exerts anti-inflammatory effects through inhibition of the TLR4/MyD88/NF-κB signaling pathway (102). GX-50, a compound derived from Sichuan pepper, exhibits promising anti-inflammatory and AD therapeutic effects (103). Research has shown that GX-50 effectively inhibits Aβ-induced TLR4 activation, preventing the recruitment of MyD88 and TNF receptor associated factor 6. This ultimately suppresses the NF-κB and MAPK signaling pathways, demonstrating potent anti-inflammatory activity (104). WD repeat and FYVE domain-containing 1 (WDFY1), a pivotal adaptor molecule in the TLR3/TLR4 signaling pathway, facilitates the recruitment of the downstream molecule TRIF found on intracellular vesicles, leading to a pro-inflammatory effect (105,106). Forsythoside B (FTS-B), a phenylethanoid glycoside derived from *Forsythiae fructus*, has been found to possess significant anti-inflammatory properties and exhibit neuroprotective benefits in AD (107). *In vivo* study has revealed that FTS-B can ameliorate cognitive impairment, mitigate pathological changes and decrease the production of pro-inflammatory cytokines in mice with AD (108). Consistent with these findings, FTS-B has been shown to suppress the inflammatory response of LPS-induced BV-2 microglia and hippocampal HT22 cells *in vitro* by blocking the WDFY1/TLR3/NF-κB signaling pathway (108).

Tanshinone IIA (Tan IIA) is a lipophilic diterpenoid compound derived from *Salvia miltiorrhiza* Bunge with significant anti-inflammatory and antioxidant properties (109), making it beneficial in attenuating the progression of AD. Research has demonstrated that Tan IIA can effectively intervene in AD mouse models induced by the injection of $A\beta_{1-42}$ into the hippocampal region. It inhibits the expression of

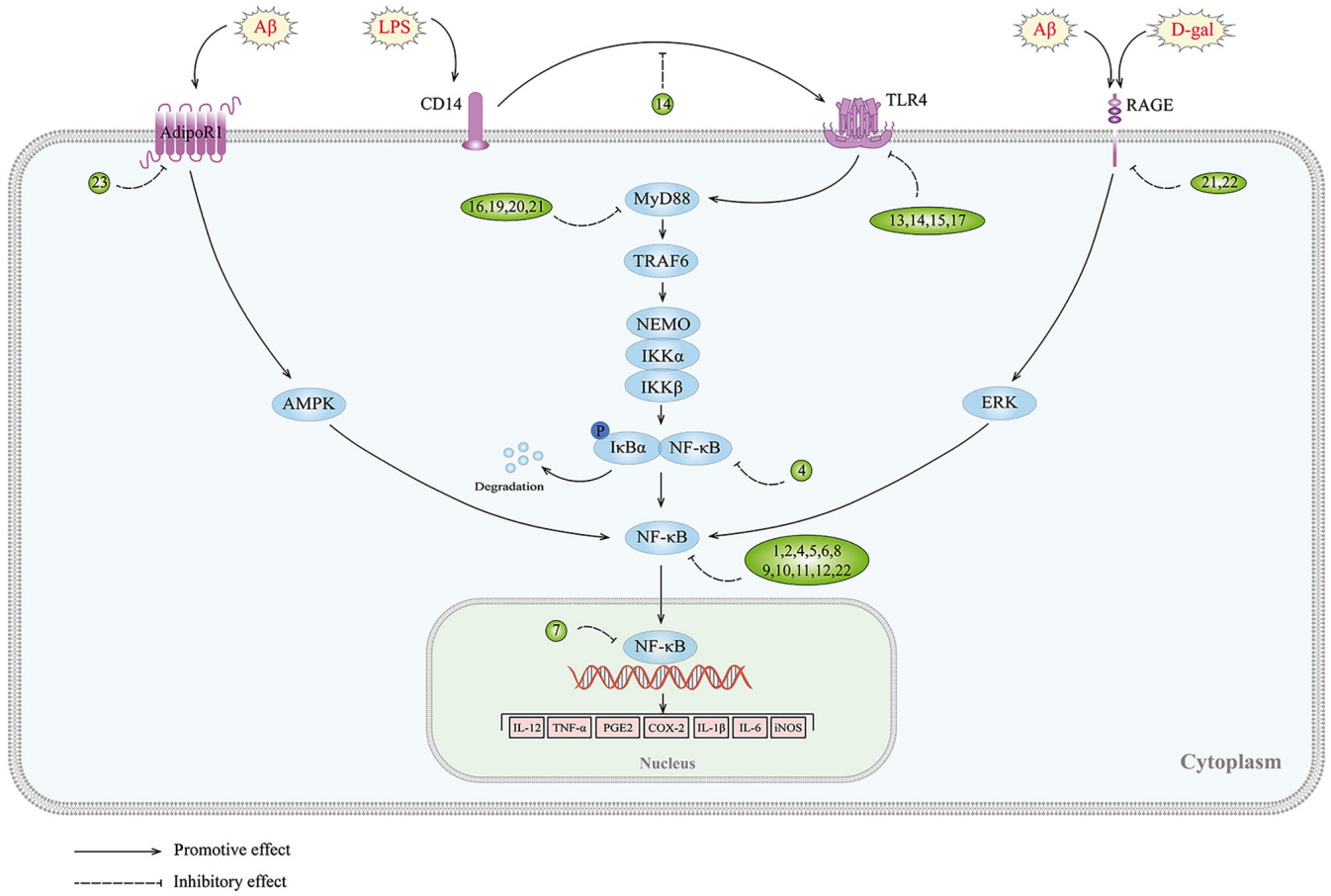


Figure 1. NF-κB signaling pathway and targets of inhibitors against neuroinflammation in AD. 1, rutin; 2, piperlongumine; 3, bee venom; 4, punicalagin; 5, tenuifolin; 6, D4 (a novel piperine derivative); 7, ethanol extract of *Bupleurum falcatum*; 8, macasiamenene F; 9, miconazole; 10, LD55; 11, the p65 binding domain of glucocorticoid-induced leucine zipper; 12, K284-6111; 13, epigallocatechin-3-gallate; 14, genistein; 15, oxysophoridine; 16, dihydromyricetin; 17, Gx-50; 18, protosappanin A; 19, icariside II; 20, ATP50-3; 21, DL0410; 22, tanshinone IIA; 23, APN; Aβ, amyloid β; LPS, lipopolysaccharide; D-gal, D-galactose; RAGE, receptor for advanced glycation end products; TLRs, Toll-like receptors; AMPK, adenosine 5'-monophosphate-activated protein kinase; MyD88, myeloid differentiation factor 88; TRAF6, TNF receptor associated factor 6; NEMO, NF-κB essential modulator; IKK, IκB kinase.

pro-inflammatory cytokines such as IL-1β and IL-6, reduces the number of microglia, lowers levels of complement molecules and improves local brain tissue inflammation (110). Similar findings were observed in AD models induced by Aβ, where Tan IIA was found to downregulate NF-κB p65 levels, thus inhibiting neuroinflammation (111,112). RAGE is implicated in Aβ-induced neuroinflammation and Tan IIA was also found to improve cognitive impairment and neuroinflammation by inhibiting RAGE/NF-κB signaling pathway, which is known to be involved in Aβ-induced neuroinflammation (113). Evidence suggests that Tan IIA provides significant anti-inflammatory benefits, leading to cognitive improvement and neuroprotection in the presence of AD. However, the clinical application of Tan IIA is limited due to its poor water solubility and short half-life (114,115). To address this issue, scientists have discovered that using chitosan as a carrier for loading Tan IIA (CS@TanIIA) can protect *Caenorhabditis elegans* from AD damage (116). The chitosan coating effectively enhances the protective effect of Tan IIA against AD by increasing its solubility. As a result of this improvement, Tan IIA has great potential for clinical application.

Adiponectin (APN) is an adipokine that is produced by adipocytes that binds to the AdipoR1 and AdipoR2 receptors (117). In aged mice, chronic deficiency of APN has been associated with cognitive impairment and the development of AD-like symptoms (118). It has also been revealed that APN deficiency exacerbates microglia activation and neuroinflammation in APN 5XFAD mice (119). Pre-treatment with APN can inhibit the release of TNFα and IL-1β in AβO-induced BV2 cells by activating the AdipoR1/Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/NF-κB signaling pathway, thereby ameliorating neuroinflammation (120). This research highlights the potential therapeutic benefits of APN in the prevention and treatment of AD (Fig. 1 and Table I).

*Mitogen-activated protein kinase (MAPK).* It is widely recognized that MAPKs, which include p38 MAPK, ERK, and c-Jun NH2-terminal kinases (JNK), as well as their isoforms (121), play a critical role in the regulation of various biological processes, including proliferation, differentiation, apoptosis and inflammation in mammalian cells (122). The MAPK signaling cascade comprises a MAPKK kinase, a MAPK kinase, and a MAP kinase (123) that respond to both internal and external stimuli, such as growth factors, cytokines, oxidation, and endoplasmic reticulum stress. Activation of the MAPK signaling pathway has been observed in the brains of patients with AD (124,125) and animal models (126). *In vitro* studies have shown that stimulation of Aβ induces the activation of this pathway in glial cell cultures, indicating its

Table I. Drugs that prevent and treat Alzheimer's disease through the NF-κB signaling pathway.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Sun *et al*, 2021 | Rutin/- | Tau-P301S mice | Tau oligomers-induced primary microglia | *In vivo:* 100 mg/kg-30 days *In vitro:* 8 $\mu$M-24 h | ↓: Tau aggregation, tau-mediated cytotoxicity, IL-1β, TNF-α, tau oligomer-induced toxicity, tau pathology, GFAP, Iba-1, IKK-β, p-P65/P65, synapse loss, microglial synapse engulfment ↑: microglial engulfment of extracellular tau, PP2A | NF-κB | (51) |
| Gu *et al*, 2018 | PL/*Piper longum* | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 1.5,3 mg/kg; 7 days *In vitro:* 0.5, 1, 2.5 $\mu$M; 18 h | ↓: Aβ1-42, activities of β-secretase and γ-secretase, APP, BACE1, COX-2, iNOS, GFAP, Iba-1, NF-κB translocation, phosphorylated-IκB, TNF-α, IL-1β, IL-6 ↑: neuronal survival | NF-κB | (53) |
| Gu *et al*, 2015 | BV/Bee | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 0.8, 1.6 $\mu$g/kg; 7 days *In vitro:* 0.5, 1, 2 $\mu$g/ml; 48 h | ↓: Aβ1-42, β-secretase and γ-secretase, APP, BACE1, COX-2, iNOS, GFAP, Iba-1, neuronal death, NF-κB translocation, p-IκB | NF-κB | (55) |
| Kim *et al*, 2017 | PUN/ pomegranate | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 1.5 mg/kg; 7 days *In vitro:* 10, 20, 50 $\mu$M; 24 h | ↓: Aβ1-42, BACE1, GFAP, Iba-1, TNF-α, IL-1β, IL-6, MDA, ROS ($H_2O_2$), COX-2, iNOS, NF-κB translocation, p-IκB, NF-κB DNA binding activity ↑: GSH/GSSG | NF-κB | (57) |
| Chen *et al*, 2020 | TEN/ *Polygala tenuifolia* Willd | - | $A\beta_{42}$-induced BV2 cells | *In vitro:* 1, 5, 10 $\mu$M; 24 h | ↓: TNF-α, IL-1β, IL-6, COX-2, iNOS, NF-κB translocation | NF-κB | (58) |
| Shahbazi *et al*, 2020 | D4/black and white pepper | - | LPS-induced human microglia clone 3 | *In vitro:* 0.86 $\mu$M; 24 h | ↓: NO, iNOS, TNF-α, IL-1β, PPAR-γ, IKK-α, IkB-α, NF-kB p65 | NF-κB | (61) |

Table I. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Park *et al*, 2015 | BFE/BF | LPS-induced C57BL/6 mice | LPS-induced BV2 cells | *In vivo:* 30 mg/kg; 3 days *In vitro* 10 $\mu$g/ml; 4 h | ↓: NO, iNOS, TNF-α, IL-1β, IL-6, NF-κB p65/RELA, GFAP, Iba-1 | NF-κB | (63) |
| Leláková *et al*, 2020 | MF/*Macaranga siamensis* | - - | LPS-induced THP-1 and THP-1-XBlue™-MD2-CD14 human monocytes, BV2 mouse microglia, and an *ex vivo* model of brain-sorted mouse microglia | *In vitro:* 1 $\mu$mol/l; 18 h | ↓: TNF-α, IL-1β, NF-κB, AP-1, degradation of IκBα | NF-κB | (64) |
| Yeo *et al*, 2020 | miconazole (MCZ)/- | LPS-induced C57BL 6/N mice $A\beta_{1-42}$-induced mice with AD | LPS-induced BV2 cells | *In vivo:* 40 mg/kg; 7/14 days *In vitro:* 1.25, 2.5, 5, 10 $\mu$M; 24 h | ↓: TNF-α, IL-1β, IL-6, COX-2, iNOS, GFAP, Iba-1, NO, p-IκB, NF-κB translocation | NF-κB | (66) |
| Solberg *et al*, 2014 | LD55/- | AβPP/PS-1 transgenic mice with AD | - | *In vitro:* a diet containing 100 ppm LD55; 12 months | ↓: Aβ plaques, activated microglia | NF-κB | (67) |
| Lindsay *et al*, 2021 | GA/GILZ | 5XFAD mice | - | *In vivo:* 100 $\mu$l GA; alternate days for 6 weeks | ↓: Aβ plaque burden, NF-κB p65, IL-1β, IL-12, IL-6, IFN-γ, GFAP, Iba-1, CD14, TLR-2, TLR-4 | NF-κB | (68) |
| Choi *et al*, 2018 | K284-6111/- | $A\beta_{1-42}$-induced mice with AD | LPS-induced BV2 cells | *In vivo:* 3 mg/kg; 4 weeks *In vitro:* 0.5, 1, 2 $\mu$M; 24 h | ↓: CHI3L1, iNOS, GFAP, Iba-1, TNF-α, IL-1β, IL-6, Aβ1-42, APP, BACE1, C99, p-IκB, NF-κB translocation | inactivation of NF-κB-mediated CHI3L1 | (69) |
| Ham *et al*, 2020 | | Tg2576 mice | Aβ-induced BV2 cells | *In vivo:* 3 mg/kg; 4 weeks *In vitro:* 0.5, 1, 2 $\mu$M; 24 h | ↓: Aβ1-42, Aβ1-40, APP, BACE1, β-secretase, COX-2, iNOS, GFAP, Iba-1, Cd86, p-IκBα, p-ERK1/2, p-JNK, CHI3L1, PTX3 | ERK-mediated PTX3 and NF-κB | (16) |

Table I. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Lian *et al*, 2017 | DL0410/- | D-gal-induced ICR mice | - | *In vivo:* 1, 3, 10 mg/kg; 4 weeks | ↓: AChE activity, AGEs, MDA, mitochondria structure, Iba-1, GFAP, RAGE, p-P65, COX2, iNOS, p-JNK, cleaved caspase 3, cleaved PARP ↑: ACh level, TEACl, activities of catalase, GPx, SOD, OPR, the number of synapses | RAGE/ NF-κB | (70) |
| Zhong *et al*, 2019 | EGCG/green tea | APP/ PS1 double transgenic mice with AD | LPS-induced BV2 cells $A\beta_{1-42}$-induced primary microglia | *In vivo:* 2 mg/kg; 4 weeks *In vitro:* 10 $\mu$M; 1 h | ↓: caspase-1 p20, NLRP3, caspase-11 p26, TLR4, p-IKK/ IKK, p-NF-κB/ NF-κB, Iba-1, IL-1β, IL-18 | TLR4/ NF-κB | (80) |
| Zhou *et al*, 2014 | Gen/SIF | - | $A\beta_{25-35}$-induced BV2 cells | *In vitro:* 12.5, 25, 50, 100, 200 $\mu$M; 26 h | ↓: IL-1β, iNOS, TLR4, NF-κB p65, NF-κB p50, DNA-binding activity of NF-κB ↑: cell viability, IL-10 | TLR4/ NF-κB | (81) |
| Chen *et al*, 2021 | Oxysophoridine/*Sophora alopecuroides* L. seeds | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 0, 2.5, 5, 10, 20, 40 $\mu$M; 48 h | ↓: MDA, TNF-α, IL-1β, TLR4, MyD88, NF-κB p65 ↑: activities of GPx, CAT, and SOD | TLR4/ NF-κB | (82) |
| Zeng *et al*, 2012 | PTA/ *Caesalpinia sappan* L. | - | LPS-induced BV2 cells | *In vitro:* 5, 10, 25, 50 $\mu$M; 10 min | ↓: Total ROS, gp91 phox, MDA, iNOS, NO, Nitrotyrosine, Iba-1, p-NF-κB p65 on serine-536, p65 and p50 translocations, IKKα/β, p-IκB, the interaction of TLR4 with MyD88, IRAK1 and TRAF6, interaction of LPS with TLR4 ↑: synapse remodeling | CD14/TLR4-dependent NF-κB | (88) |

Table I. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Capiralla *et al*, 2012 | Resveratrol/ red wines | APP/ PS1 double transgenic mice with AD | LPS-induced BV2 cells | *In vivo:* 350 mg/kg; 15 weeks *In vitro:* 100 mM; 30 min | ↓: IL-6, M-CSF, MCP-1, MCP-5, CD54, IL-1ra, IL-27, TNF-α, p-Akt, COX-2, iNOS, STAT1, STAT3, TLR4, Iba-1 | TLR4/ NF-κB/ STAT | (90) |
| Zhou *et al*, 2019 | ICS II/ *Epimedium brevicornum* Maxim | LPS-induced SD rats | - | *In vivo:* 3, 10 mg/kg; 7 days | ↓: neuronal changes, neuronal degeneration, GFAP, Iba-1, COX-2, IL-1β, TNF-α, TLR4, MyD88, TRAF6, p-NF-κB ↑: IκB-α degradation | TLR4/ MyD88/ NF-κB | (94) |
| Zhang *et al*, 2021 | DL0410/- | D-gal-induced SD rats | LPS-induced BV2 cells | *In vivo:* 1,3, 10 mg/kg-8 weeks *In vitro:* 1-30 $\mu$M-2 h | ↓: MDA,AGEs, SOD1, SOD2, Iba-1, GFAP, TNF-α, IL-1β, IL-6, COX2, iNOS, TLR, MyD88, p-IκBα and NF-κB p65, NF-κB translocationp65, NO, TRAF6, p-IKKα/β, p-IκBα ↑: PSD95, IL-10, claudin-1, claudin-5, occludin, CX43, ZO-1 | TLR4/ MyD88/ NF-κB | (97) |
| Zhong *et al*, 2020 | ATP50-3/ *Acorus tatarinowii* | - | LPS-induced BV2 cells | *In vitro:* 2.5,5, 10 $\mu$M-2 h | ↓: TNF-α, IL-1β, IL-6, COX-2, iNOS, CD11b, TLR4, MyD88, IKKα/β, IκBα, NF-κB p65, PI3K, Akt | TLR4-mediated MyD88/ NF-κB and PI3K/ Akt | (100) |
| Jing *et al*, 2019 | DHM/ *Ampelopsis grossedentata* | - | LPS-induced BV2 cells | *In vitro:* 20, 40, 80, 100 mg/l; 48 h | ↓: TNF-α, IL-1β, IL-6, COX-2, iNOS, p-p65, p-IκBα, TLR4, MyD88 ↑: BV-2 microglia viability | TLR4/ MyD88/ NF-κB | (102) |
| Shi *et al*, 2016 | Gx-50/ Sichuan pepper | APP-Tg mice | $A\beta_{42}$-induced BV2 cells and primary microglia | *In vivo:* 1 mg/kg; 2 months *In vitro:* 1 $\mu$M; 30 min | ↓: TNF-α, IL-1β, NO, PGE2, iNOS, COX2, p-IκB, NF-κB translocation, p-ERK1/2, p-p38, p-JNK, TLR4, MyD88, TRAF6 | TLR4-mediated NF-κB and MAPK | (104) |

Table I. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Kong *et al*, 2020 | FTS-B/ *Forsythiae fructus* | APP/ PS1 double transgenic mice with AD | LPS-induced BV2 cells | *In vivo:* 10 , 40 mg/kg; 36 days *In vitro*: 1, 2.5 $\mu$M; 3 h | ↓: Aβ deposition, JIP3, p-JNK/JNK, p-APP/APP, Aβ, TNF-α, IL-1β, IL-6, IL-8, IL-12, ELKS, p-IKK (α+β), p-IκBα, p-NF-κB (Ser536), Iba1, GFAP, NO, iNOS, apoptosis rate of the HT22 cells ↑: TLR3, p-IRF3/ IRF3, IFN-β, WDFY1, p-IRF3, cell viability | WDFY1/ TLR3/ NF-κB | (108) |
| Lu *et al*, 2016 | Tan IIA/ *Salvia miltiorrhiza* | $A\beta_{1-42}$-induced AD rats | - | *In vivo:* 8 mg/kg; 30 days | ↓: A β, IL-1β, IL-6, GFAP, CD11b, C1q, C3c, C3d | - | (110) |
| Li *et al*, 2015 | | Aβ-induced AD rats | - | *In vivo*: 50 mg/kg; 15 days | ↓: iNOS, MMP-2, NF-κB p65 | NF-κB | (351) |
| Maione *et al*, 2018 | | $A\beta_{1-42}$-induced mice with AD | - | *In vivo:* 1, 3, 10 mg/kg; 21 days | ↓: GFAP, S100β, COX-2, NF-κB p65 | NF-κB | (112) |
| Ding *et al*, 2020 | | APP/ PS1 double transgenic mice with AD | $A\beta_{1-42}$-induced BV2 cells | *In vivo:* 5, 20 mg/kg; 30 days *In vitro:* 1, 10 $\mu$M; 30 min | ↓: Loss of Syn and PSD-95, Aβ1-40, Aβ1-42, the number of activated microglia, Iba-1, GFAP, TNF-α, IL-6, IL-1β, expression of RAGE, p-IκBα, NF-κB p65 | RAGE/ NF-κB | (113) |
| Jian *et al*, 2019 | APN/- | 5XFAD mice APN-/- 5XFAD mice | AβO-induced BV2 cells | *In vitro:* 10 $\mu$g/ml- 2 h | ↓: TNF-α, IL-1β, p-NF-κB p65S536, NF-κB p65, Aβ plaques ↑: p-AMPKT172, GFAP, Iba1 | AdipoR1-AMPK-NF-κB | (120) |

PL, piperlongumine; BV, bee venom; PUN, punicalagin; TEN, Tenuifolin; D4, a novel piperine derivative; BFE, ethanol extract of BF; BF, Bupleurum falcatum L.; MF, macasiamenene F; MCZ, miconazole; GA, the p65 binding domain of GILZ; GILZ, glucocorticoid induced leucine zipper; K284-6111, 2-({3-[2-(1-cyclohexen-1-yl)ethyl]-6,7-dimethoxy-4-oxo-3,4-dihydro-2-quinazolinyl}sulfanyl)-N-(4-ethylphenyl) butanamide; EGCG, epigallocatechin-3-gallate; Gen, genistein; SIF, Soybean isoflavone; PTA, protosappanin A; ICS II, icariside II; DHM, dihydromyricetin; FTS-B, forsythoside B; Tan IIA, tanshinone IIA; APN, Adiponectin; p- phosphorylated; AD, Alzheimer's disease; Aβ, amyloid β; APP/PS1, amyloid-β protein/presenilin-1; 5XFAD, 5X familial Alzheimer's disease; AChE, acetylcholinesterase; APN, Adiponectin; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; BACE1, β-site amyloid precursor protein cleaving enzyme 1; COX-2, cyclooxygenase-2; CHI3L1, chitinase-3 like-protein-1; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; JNK, c-Jun NH2-terminal kinases; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; MAPK, mitogen-activated protein kinase; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; PTA, protosappanin A; PI3K, phosphoinositide 3-kinase; PPARs, peroxisome proliferator-activated receptors; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLRs, Toll-like receptors; WDFY1, WD repeat and FYVE domain-containing 1; NF-κB, nuclear factor-kappa-B; Iba-1, ionized calcium binding adaptor molecule 1; STAT3, signal transducers and activators of transcription 3; AP-1, activator protein 1; PGE2, prostaglandin E2.

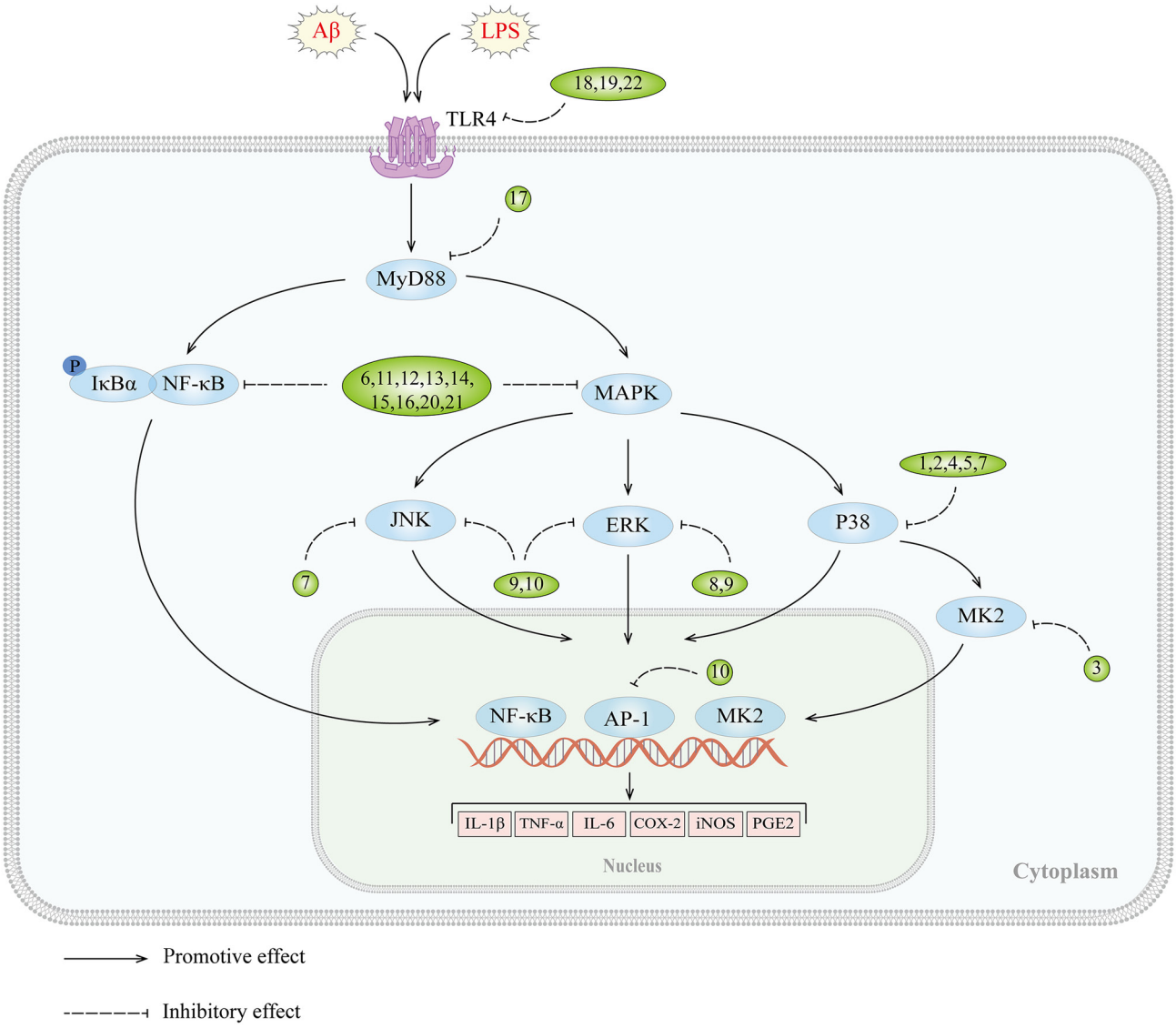


Figure 2. MAPK signaling pathway and targets of inhibitors against neuroinflammation in AD. AD, Alzheimer's disease; 1, MW01-2-069A-SRM; 2, MW181; 3, MMI-0100; 4, methanol extracts of *Piper sarmentosum* roots; 5, EGB761; 6, cryptolepine; 7, VB-037; 8, dexmedetomidine; 9, *Hominis placenta*; 10. BJe; 11, diammonium glycyrrhizinate; 12, tripterygium glycosides; 13, LX007; 14, pseudane-VII; 15, sorbinil and zopolrestat; 16, Artemisiae Iwayomogii Herba; 17, tectorigenin; 18, circumdatin D; 19, 1-O-acetylbritannilactone; 20, *Ganoderma lucidum* extract GLE; 21, Atractylodis Rhizoma Alba ethanolic extract; 22, ulmoidol; Aβ, amyloid β; LPS, lipopolysaccharide; TLRs, Toll-like receptors; MyD88, myeloid differentiation factor 88; IKK, IκB kinase; JNK, c-Jun NH2-terminal kinases; MK2, MAPK-activated protein kinase II; AP-1, activator protein 1.

involvement in the development of AD (127-129). Inhibition of tau kinases, such as p38 MAPK, has been shown to improve cognitive deficits and reduce tau pathology in AD (130). Furthermore, blocking the ERK pathway can reverse mitochondrial dysfunction in AD (131,132), while specific JNK inhibitors can enhance synaptic function (133). Of note, the MAPK signaling pathway can also regulate the neuroinflammatory response of microglia. Aβ-induced production of inflammatory cytokines and ROS can activate this pathway, leading to more severe inflammation. A number of *in vitro* experiments have demonstrated that inhibition of the MAPK signaling pathway can suppress neuroinflammation in BV2 microglia (134,135), highlighting its potential as an effective strategy for treating AD (Fig. 2 and Table II).

*P38 MAPK*. P38, a member of the P38 MAPK subfamily, has been found to be activated in both AD brain tissue samples (136) and animal models (126) of AD. Additionally, study has shown that the absence of P38 MAPK attenuates amyloid-like pathology in AD models (137). Specifically, P38α MAPK is thought to play a crucial role in the dysregulation of microglia and neuroinflammation during AD progression, making it a recognized target for AD treatment (130,138,139). Thus, targeting P38α MAPK may offer a promising therapeutic strategy to address the underlying neuroinflammatory processes in AD.

Several inhibitors of the p38α MAPK signaling pathway, including natural product extracts, and organic compounds, have shown promise in reducing neuroinflammation and treating AD. Both preclinical and clinical trials have evaluated the pharmacological effects of these inhibitors in the brain. Selective p38α MAPK inhibitors, such as MW01-2-069A-SRM (140) and MW181 (141), which are able to penetrate the BBB, have demonstrated potent inhibitory effects on neuroinflammation. Additionally, VX-745, a

Table II. Drugs that prevent and treat Alzheimer's disease through the MAPK signaling pathway.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Munoz *et al*, 2007 | MW01-2-069A-SRM/- | $A\beta_{1-42}$-induced mice with AD | - | *In vivo:* 2.5 mg/kg; two weeks | ↓: IL-1β, TNFα, S100B | p38 MAPK | (140) |
| Maphis *et al*, 2016 | MW181/- | hTau mice LPS-induced MK2-/- mice | $Cx3cr1^{-/-}$CM-induced primary neurons and microglia | *In vivo:* 1 mg/kg; 14 days *In vitro:* 2 μM; 30 min | ↓: p-tau, p-p38α MAPK (T180/Y182), tau (AT8 site), p-pATF2(T71), pATF2, pMK2, IFNγ, IL-1β, IL-6, TNFα, p38α MAPK ↑:synaptophysin, YM1,ARG1 | p38 MAPK | (141) |
| Alam *et al*, 2015 | VX-745/- | Tg2576 mice | - | *In vivo:* 0.5, 1.5, 4.5 mg/kg; 2 weeks | ↓: amyloid plaque, IL-1β ↑: PSD95 | p38 MAPK | (143) |
| Jiang *et al*, 2019 | MMI-0100/- | $A\beta_{1-42}$-induced mice with AD | LPS-induced BV2 cells | *In vivo:* 2 μl; the lateral ventricle; 0.5 μl/CA1 side; 15 min 25 nmol; 10 μl; intranasal infusion; 1 min *In vitro:* $10^{-5}$-$10^{-8}$ M; 24 h | ↓: CD11b, GFAP, IL-6, IL-1β, TNF-α, iNOS, p-MK2 | p38 MAPK/ MK2 | (147) |
| Chan *et al*, 2019 | RMEOH/PS | - | Aβ-induced BV2 cells | *In vitro:* 6.25 μg/ml; 4 h | ↓: IL-1β, IL-6, TNF-α, NO, p38α MAPK | p38 MAPK | (151) |
| Meng *et al*, 2019 | EGB 761/ *Ginkgo biloba* | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 10, 90 μg/ml; 12 h | ↓: NF-κB translocation, IL-1β, TNF-α, p38 MAPK | p38 MAPK | (153) |
| Olajide *et al*, 2013 | Cryptolepine/ *Cryptolepis sanguinolenta* | - | LPS-induced primary microglia and BV2 cells | *In vitro:* 2.5, 5 μM; 30 min | ↓: TNF-α, IL-6, IL-1β, PGE2, COX2, mPGES-1, iNOS, NO, p-p38 MAPK, MAPKAPK2, NF-κB p65 translocation | NF-κB and p38 MAPK | (157) |

Table II. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Chiu *et al*, 2019 | VB-037/ quinoline compounds | - | LPS/IFN-γ-induced BV2 cells Aβ-GFP SH-SY5Y cells | *In vitro:* 10 $\mu$M; 8 h | ↓: Aβ aggregation, ROS, NO, Iba1, AChE, caspase1, IL-1β, JNK, Jun proto-oncogene, AP-1 transcription, JUN ↑: HSP27, cell viability | P38, JNK | (155) |
| Ho *et al*, 2020 | AZD6244/- | - | acrolein-induced BV2 cells | *In vitro:* 10 $\mu$M; 16 h | ↓: p-ERK, TNF-α, COX-II, HO-1 | MEK-ERK | (163) |
| Qiu *et al*, 2020 | dexmedetomidine/- | - | LPS-induced BV2 cells | *In vitro:* 1, 5, 10 $\mu$M; 0, 6, 12, 24 h | ↓: NO, morphological changes in BV2 cells, TNF-α, iNOS, p-ERK1/2 ↑: IL-10, CD206, microglial M2 polarization | ERK | (164) |
| Lee *et al*, 2013 | HP/placenta | - | LPS-induced BV2 cells | *In vitro:* 50 $\mu$M; 2 h | ↓: p-JNK, p-ERK, p-AKT, iNOS, NO, COX2 | JNK and ERK | (166) |
| Currò *et al*, 2016 | BJe/ Bergamot juice | - | $A\beta_{1-42}$-induced THP-1 cells | *In vitro:* 0.05, 0.1 mg/ml; 16 h | ↓: IL-6, IL-1β, p-p54, ERK 1/2, p46 JNK, AP-1 DNA binding activity | MAPK/ AP-1 | (168) |
| Tang *et al*, 2021 | TGs/- | $A\beta_{25-35}$-induced mice with AD | $A\beta_{25-35}$-induced PC12 cells | *In vivo:* 0.25 mg/ 10 g.d; 28 days *In vitro:* 25 $\mu$g/l; 24 h | ↓: Aβ25-35, p-Tau, CD11b, p-IκBα, p-P38, caspase-1, COX2, iNOS, IL-1β, TNF-α, NO ↑: The neuron number | NF-κB and MAPK | (172) |
| Cao *et al*, 2018 | LX007/- | - | LPS-induced primary microglia | *In vitro:* 10, 20, 30 $\mu$M; 1 h | ↓: NO, iNOS, PGE2, COX-2, IL-1β, IL-6, TNF-α, p-ERK1/2, JNK, p38, p-IκBα, IκBα degradation, p65 | NF-κB and MAPK | (173) |
| Kim *et al*, 2018 | Pseudane-VII/*Pseudoalteromonas* sp.M2 | - | LPS-induced BV2 cells | *In vitro:* 0.5, 1, 2.5, 5 $\mu$M; 2 h | ↓: iNOS, COX-2, IL-1β, p-p65, ERK, p38 MAPK, JNK1/2, Iba-1 | NF-κB and MAPK | (174) |
| Zhao *et al*, 2013 | DG/GA | $A\beta_{1-42}$-induced mice with AD | $A\beta_{1-42}$-induced BV2 cells | *In vivo:* 10 mg/kg; 14 days *In vitro:* 0.001 mg/ml; 1 h | ↓: TNF-α, COX-2, iNOS, IL-1β, COX-2, iNOS, GFAP, Iba-1, p65 translocation, p-ERK, JNK, p38 ↑: IL-10 | MAPK and NF-κB | (175) |

Table II. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Song *et al*, 2017 | Sor and Zol/- | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 20 $\mu$M; 1 h | ↓: TNF-α, IL-1β, IL-6, NF-κB p65 translocation, p-IKKβ, p-IκB, p-NF-κB, p-JNK, p-p38, p-ERK, ROS, p-PKCα/β, PKCδ, PKCζ/λ, PKCmu subtypes | ROS/PKC-dependent NF-κB and MAPK | (177) |
| Ju *et al*, 2021 | AIH/- | LPS-induced C57BL 6J mice | LPS-induced BV2 cells | *In vivo:* 10, 30, 100 mg/kg; 14 days *In vitro:* 1, 10, 100 $\mu$g/ml; 24 h | ↓: NO, iNOS, COX2, TNF-α, IL-6, p-p65, p-p38, p-JNK, NLRP3, Iba-1 | NF-κB and MAPK | (180) |
| Hilliard *et al*, 2020 | GLE/*Ganoderma lucidum* | - | LPS-induced BV2 cells | *In vitro:* 0.5 mg/ml; 1 h | ↓: G-CSF, IL1α, MCP-5, MIP3, RANTES, CHUK, NFκB1/p50, IKBKE | NF-κB and MAPK | (181) |
| Jeong *et al*, 2019 | ARAE/ARA | - | LPS-induced BV2 cells | *In vitro:* 10, 50, 100 $\mu$g/ml; 18 h | ↓: NO, TNF-α, IL-6, IL-1β, iNOS, COX-2, HO-1, NF-κB p65 translocation, p-IκBα, IκBα degradation, p-ERK, p-p38, p-JNK | NF-κB and MAPK | (134) |
| Tang *et al*, 2021 | ABL/*Inula britannica* L. | - | LPS-induced BV2 cells | *In vitro:* 1, 3, 10 $\mu$M; 24 h | ↓: NO, TNF-α, PGE2, iNOS, CD14, NF-κB p65, IRAK1, p-p38 ↑: HO-1, Arg-1, IL-10 | TLR4-mediated NF-κB and MAPK | (185) |
| Han *et al*, 2021 | ULM/*Eucommia ulmoides* Oliv | - | LPS-induced BV2 cells | *In vitro:* 1, 3, 10 $\mu$M; 24 h | ↓: TNF-α, IL-1β, IL-6, PGE2, COX-2, iNOS, p-IκBα, p-p38, p-ERK, p-JNK, CD14, TLR4, MD2, MyD88, TRAF6, TAK1 | TLR4-mediated NF-κB and MAPK | (188) |
| Zhang *et al*, 2020 | Circumdatin D/*Aspergillus ochraceus* | C4176 nematodes | LPS-induced BV2 cells and primary microglia | *In vivo:* 50, 100, 200 $\mu$M; 16 h *In vitro:* 10, 20, 50 $\mu$M; 6 h | ↓: NO, AChE, TNF-α, IL-1β, iNOS, COX-2, neuron death, TLR4, MyD88, NF-κB p65, p-IKK, p-IκB, p-MAPK, p-STAT3, STAT3 translocation, p-JAK2 | TLR4-mediated NF-κB, MAPK andJAK/STAT | (189) |

Table II. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Lim *et al*, 2018 | TEC/ *Pueraria thunbergiana* Benth | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 5, 10 mg/kg; 5 days *In vitro:* 12.5, 25, 50, 100 $\mu$M; 24 h | ↓: NO, PGE2, iNOS, COX-2, TNF-α, IL-6, NF-κB p65, p-ERK, p-JNK, Iba-1, TLR4, MyD88 | TLR4-MyD88-mediated inhibition of ERK/ JNK and NF-κB | (192) |

RMEOH, methanol extracts of PS roots; PS, Piper sarmentosum Roxb; HP, Hominis placenta; TGs, Tripterygium glycosides; LX007, 4-[(5-bromo-3-chloro-2-hydroxybenzyl) amino]-2-hydroxybenzoic acid; DG, diammonium glycyrrhizinate; GA, glycyrrhizin acid; Sor, sorbinil; Zol, zopolrestat; AIH, Artemisiae Iwayomogii Herba; GLE, Ganoderma lucidum extract; ARAE, ARA ethanolic extract; ARA, Atractylodis Rhizoma Alba; ABL, 1-O-acetylbritannilactone; ULM, ulmoidol; TEC, tectorigenin; AD, Alzheimer's disease; Aβ, amyloid β; AChE, acetylcholinesterase; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; HO-1, Haem oxygenase-1; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; JNK, c-Jun NH2-terminal kinases; JAK2, Janus kinase 2; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; MAPK, mitogen-activated protein kinase; MAPKKK, MAPKK kinase; MK2, MAPK-activated protein kinase II; MEK, mitogen-activated extracellular signal-regulated kinase; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; PKC, protein kinase C; PKA, protein kinase A; ROS, reactive oxygen species; TLRs, Toll-like receptors; p-, phosphorylated; NF-κB, nuclear factor-kappa-B; Iba-1, ionized calcium binding adaptor molecule 1; STAT3, signal transducers and activators of transcription 3; AP-1, activator protein 1; PGE2, prostaglandin E2.

small molecule inhibitor of p38α MAPK, has emerged as a promising candidate for anti-inflammatory therapy and is currently undergoing pilot trials for the treatment of rheumatoid arthritis (142). Notably, preclinical studies have revealed that VX-745 exerts its anti-neuroinflammatory effects by selectively targeting of p38α MAPK, resulting in a reduction of IL-1β levels in the hippocampus of aged rats (143). This finding highlights the potential utility of VX-745 as a therapeutic strategy for neurological disorders characterized by neuroinflammation (143). MAPK-activated protein kinase II (MK2), a downstream kinase of p38 MAPK (144), is activated and upregulated in AD mouse models and is associated with Aβ deposition, microglia activation, and the upregulation of pro-inflammatory cytokines (145). Targeting MK2 may be a promising therapeutic strategy for AD. MMI-0100, a cell-penetrating peptide inhibitor of MK2 with anti-inflammatory activity (146), has been shown to inhibit LPS-induced microglia activation and significantly reduce pro-inflammatory cytokine production in mice by inhibiting MK2 phosphorylation (147). Furthermore, intranasal administration of MMI-0100 can overcome the challenge of failed AD treatments with large molecule protein or peptide drugs due to its ability to penetrate the BBB (148,149).

*Piper sarmentosum* Roxb. (PS) is a medicinal plant (150) that has been the subject of recent research investigating potential therapeutic applications in neuroinflammatory diseases. *In vitro* experiments have demonstrated that pre-treatment of BV2 microglia with methanol extracts of PS roots results in a significant reduction in Aβ-induced expression of proinflammatory cytokine mRNA and protein, thereby exerting neuroprotective effects, which is associated with the regulation of phosphorylation of p38α MAPK in microglia (151). These findings suggest that PS represents a promising option for the management of neuroinflammatory conditions. Derived from *Ginkgo biloba* leaves, EGb761 has been extensively studied for its potential in ameliorating cognitive impairment and AD (152). In a cellular model of BV-2 microglia stimulated by $A\beta_{1-42}$, EGb761 intervention effectively attenuated the concentration-dependent production of TNF-α and IL-1β and simultaneously downregulated their respective mRNA expressions (153). Additionally, the inhibition of p38 MAPK phosphorylation induced by Aβ was found to be selectively achieved by EGb761, while it had no significant impact on the expression of ERK and JNK. These results suggest that the anti-inflammatory mechanism of EGb761 may be due to the selective modulation of the p38 MAPK signaling pathway (153).

Quinoline, a heterocyclic aromatic organic compound, has attracted considerable attention for its antibacterial properties (154) and its ability to inhibit amyloid aggregation (155,156). Consequently, this framework is widely utilized in the research and design of innovative anti-inflammatory drugs. Cryptolepine, an indoloquinoline alkaloid isolated from *Cryptolepis sanguinolenta*, has demonstrated the ability to suppress LPS-induced microglia inflammation by selectively targeting the NF-κB and p38 MAPK signaling pathways (157). Similarly, VB-037 (155), a quinoline compound, has been shown to effectively mitigate BV-2 microglial activation induced by LPS/interferon-γ (IFN-γ). This attenuation is achieved by inhibiting caspase 1 activation, IL-1β expression and P38 phosphorylation, as well as by affecting the JNK, Jun oncogene and Jun signaling pathways. These findings

substantiate that VB-037 selectively regulates the P38 and JNK/MAPK signaling pathways, ameliorating neuronal damage and neuroinflammation and thereby altering the progression of AD. The multifaceted mechanism of quinoline derivatives offers several opportunities for the development of AD therapeutics (155,157).

*ERK and JNK*. The ERK/MAPK pathway and the JNK/MAPK pathway (155), which utilize ERK and JNK as their final kinases, respectively, are essential subsets of the MAPK signaling cascade that regulate neuronal development (158,159). However, dysregulation of these pathways can lead to developmental abnormalities and behavioral deficits (158,160). Notably, chronic activation of these pathways has been observed in the hippocampus of transgenic AD mouse models overexpressing Aβ (161) and in patients with AD, where elevated brain levels of p-ERK have been positively correlated with disease progression (162). This underscores its importance in AD pathogenesis and supports the idea that drugs targeting ERK represent a promising therapeutic approach for managing AD.

Numerous inhibitors of the MEK (mitogen-activated extracellular signal-regulated kinase)/ERK signaling pathway, both natural product extracts, and organic compounds, have displayed potential in reducing neuroinflammation and treating AD. Recent study has highlighted the efficacy of AZD6244 (163), an oral MEK1/2 inhibitor, in suppressing acrolein-induced neuroinflammation by modulating of the MEK/ERK signaling pathway in BV-2 cells, leading to its neuroprotective effects (163). Similarly, Dexmedetomidine (164), an α2 adrenergic receptor agonist with sedative, analgesic and anxiolytic properties, was found to upregulate anti-inflammatory cytokines and M2 phenotype markers, while downregulating pro-inflammatory cytokines, M1 phenotype markers, and p-ERK1/2 in LPS-stimulated BV2 microglia. This effect has been shown to be reversed by LM22B-10, an ERK agonist, supporting the notion that Dexmedetomidine promotes M2 polarization in microglia through modulation of the ERK signaling pathway, ultimately exerting its anti-inflammatory properties (164). *Hominis placenta* (HP) is a dried placental extract from pregnant women after delivery that has been shown to promote neural regeneration (165). Lee *et al* (166) demonstrated that pre-treatment with HP significantly inhibited the expression of iNOS and COX2 in LPS-induced BV2 cells. This anti-inflammatory effect was achieved, at least in part, through the inhibition of the ERK pathway and the phosphorylation of JNK and ERK. In addition, Bergamot juice (BJ) was found to have antibacterial properties and to exert anti-inflammatory effects (167) through its flavonoid component (BJe) (168), which was shown to partly affect the ERK signaling pathway. The critical role of monocytic cells in neuroinflammation has been underlined by their ability to cross the BBB and differentiate into microglia in the brain parenchyma (169,170). In this context, a research team found that pretreatment with BJe resulted in a concentration-dependent reduction in the upregulation of pro-inflammatory cytokine expression and a decrease in the phosphorylation levels of JNK and ERK1/2 in $A\beta_{1-42}$-induced THP-1 monocytic cells. This effect was associated with the disruption of DNA-binding activity of AP-1 (activator protein 1) and the MAPK/AP-1 pathway, thereby counteracting the pro-inflammatory activation of monocytic/microglia induced by Aβ and exerting an anti-neuroinflammatory effect (168).

*NF-κB and MAPK*. The NF-κB and MAPK signaling pathways have emerged as key regulators of pro-inflammatory mediator expression and NLRP3 inflammasome formation, both of which play a role in neuroinflammation. Therefore, targeting these signaling pathways represents a potential therapeutic approach to alleviate neuroinflammation. Notably, specific inhibitors or drugs have been found to exhibit dual targeting of both NF-κB and MAPK signaling pathways, which may provide a more robust anti-neuroinflammatory effect. This highlights the possibility of developing a combination therapy targeting multiple pathways for the treatment of neuroinflammation.

Several synthetic drugs or inhibitors have been discovered that have anti-neuroinflammatory effects by targeting the signaling pathways of NF-κB and MAPK. For example, Tripterygium (TG), a non-steroidal immunosuppressant, has been shown to have anti-inflammatory, anti-tumor and immunosuppressive properties (171). Research suggests that TG can alleviate neuroinflammation by inhibiting the NF-κB and MAPK signaling pathways, thereby reducing the expression of $A\beta_{25-35}$, p-Tau, CD11b and various pro-inflammatory cytokines in an AD model. This implies the feasibility of TG intervention in AD pathology (172). A compound called 4-[(5-bromo-3-chloro-2-hydroxybenzyl) amino]-2-hydroxybenzoic acid (LX007) (173) has been identified as a potent mitigator of microglia-induced inflammatory responses. LX007 has demonstrated a significant anti-inflammatory activity in LPS-stimulated primary microglia inflammation models by inhibiting the phosphorylation of MAPK and NF-κB p65 nuclear translocation, effectively inhibiting NO and prostaglandin E2 (PGE2) production and reducing pro-inflammatory cytokine gene and protein expression (173). These findings imply that LX007 may be a potential drug for treating inflammatory reactions. Pseudane-VII, a secondary metabolite derived from *Pseudoalteromonas sp*. M2, has been shown to possess anti-inflammatory activity (173) by inhibiting the phosphorylation of p38, ERK1/2, JNK1/2 and NF-κB. Similarly, diammonium glycyrrhizinate (DG), the salt form of glycyrrhizin acid (174), has been found to play a critical role in inhibiting $A\beta_{1-42}$-induced neuroinflammation by regulating the MAPK and NF-κB pathways (174). An *in vivo* study has revealed that DG can alleviate memory impairment in mice, inhibit activation of microglia in the hippocampus and reduce the expression and production of pro-inflammatory mediators (175). Further investigation has revealed that the anti-inflammatory effect of DG involves inhibiting the translocation of NF-κB p65 to the nucleus, as well as reducing the phosphorylation levels of ERK, JNK and p38 MAPK (175). It is notably that aldose reductase inhibitors (ARIs) exert their effects by regulating the ROS/protein kinase C (PKC)-dependent NF-κB and MAPK signaling pathways. Aldose reductase (AR), a rate-limiting enzyme in the polyol pathway of glucose metabolism, is a molecular target in various inflammatory diseases (176). An *in vitro* study was conducted to investigate the effects of typical ARIs, sorbinil (Sor) and zopolrestat (Zol) (177), on $A\beta_{1-42}$-induced BV-2 microglia. The results demonstrated that both Sor and Zol significantly

inhibited TNF-α secretion, downregulated the expression of pro-inflammatory genes and proteins via interference with the NF-κB and MAPK pathways, in addition to inhibiting the phosphorylation of several PKC subtypes (177). Notably, this inhibition of PKC was demonstrated to be mediated by reducing intracellular ROS generation (178). Taken together, these findings suggest that the anti-neuroinflammatory effects of ARIs are, at least in part, ROS/PKC dependent (177). However, further *in vivo* studies are necessary to confirm the efficacy and safety of ARIs, as well as to explore their potential for treating neurodegenerative diseases.

Traditional medicines, natural products, and their derivatives have demonstrated promising therapeutic properties for the treatment of neuroinflammation. Artemisiae Iwayomogii Herba (AIH), a traditional herb (179) utilized for the treatment of inflammatory conditions, was found to inhibit LPS-induced neuroinflammation in BV-2 microglia and mice brains (180). This effect was achieved by reducing NO production and the expression of pro-inflammatory mediators, as well preventing the formation of the NLRP3 inflammasome (180). The anti-inflammatory effect of AIH is associated with the regulation of the NF-κB and MAPK signaling pathways (180). Similarly, *Ganoderma lucidum* extract (GLE) (181) has been shown to possess neuroprotective properties (182) and has exhibited efficacy in the treatment of inflammatory diseases (183). Pretreatment with GLE downregulates the expression of pro-inflammatory genes in LPS-stimulated BV-2 microglia by modulating NF-kB and MAPK signaling pathways, thereby exerting an anti-neuroinflammatory effect (181). Atractylodis Rhizoma Alba (ARA) ethanolic extract (ARAE) (134) was also found to have anti-neuroinflammatory effects in an *in vitro* inflammatory model, associated with the inhibition of the NF-κB and MAPK signaling pathways (184). ARAE significantly decreased the production of NO and inflammatory cytokines and inhibited the expression of iNOS and COX-2. Further analysis indicated that the anti-inflammatory effects of ARAE were mainly due to inhibition of IκBα degradation, phosphorylation, and NF-κB p65 nuclear translocation, suggesting a multi-pathway approach to reducing neuroinflammation (134). Similarly, 1-O-acetylbritannilactone (also termed Inulicin; ABL), a natural product derived from *Inula britannica* L. (185) and its derivative 'compound 15' were found to inhibit neuroinflammation in LPS-induced BV-2 microglia. Compound 15 was found to block NF-κB translocation, reduce CD14 generation by TLR4 in a dose-dependent manner, and significantly inhibit p38 MAPK phosphorylation, thereby downregulating the p38 MAPK inflammatory signaling pathway. Moreover, compound 15 was found to convert BV-2 microglia from M1 to M2 phenotypes, further enhancing its ability to inhibit neuroinflammation (185). *Eucommia ulmoides* Oliver (Du Zhong) is a renowned traditional Chinese medicine containing therapeutic chemical compounds for a variety of diseases (186,187). Its active compounds possess anti-neuroinflammatory properties, with ulmoidol (ULM) (188) exhibiting the most potent anti-inflammatory activity. By interfering with TLR4 signaling, ULM inhibits downstream NF-κB and MAPK pathways, downregulates pro-inflammatory cytokine expression and production in LPS-induced BV-2 cells, thereby exerting its anti-neuroinflammatory effects (188). Another active compound, circumdatin D, extracted from *Aspergillus ochraceus*, possesses dual activity in inhibiting AChE and promoting anti-inflammatory reactions (189). It significantly inhibits NO production, TNF-α, and IL-1β release, and reduces iNOS and COX-2 expression in LPS-induced BV-2 cells by inhibiting TLR4-mediated NF-κB, MAPK, and JAK/STAT inflammatory signaling pathways. Tectorigenin (TEC), an active ingredient in a number of traditional medicines with anti-tumor (190) and antibacterial effects (191), can also be used to treat neuroinflammation. In *in vitro* experiments, TEC not only reduces NF-κB p65 subunit levels but also inhibits ERK and JNK phosphorylation (192). Notably, TEC pre-treatment inhibited TLR4, MyD88, and LPS-induced pro-inflammatory cytokine expression both *in vivo* and *in vitro*, indicating that its anti-inflammatory mechanisms are closely related to TLR4-MyD88-mediated inhibition of MAPK and NF-κB (192). These findings suggest that traditional Chinese herbal ingredients may be effective in treating neuroinflammatory diseases by inhibiting TLR4 signaling and downstream inflammatory pathways. Further studies are needed to explore their potential clinical applications and mechanisms of action *in vivo*. In summary, traditional medicines, natural products, and their derivatives have shown promise in targeting both NF-κB and MAPK signaling pathways and represent a promising therapeutic approach for managing AD.

## 3. NLRP3 inflammasome

The NLRP3 inflammasome is a multi-protein complex consisting of the regulatory subunit NLRP3, the adaptor protein apoptosis-associated speck-like protein (ASC) and the effector cysteine protease caspase-1 (192) that plays a central role in sterile inflammatory diseases by regulating the cleavage of IL-1β precursor (193). The inflammasome requires two signals for activation: The first signal triggers the synthesis of IL-1β precursor and other inflammasome components such as NLRP3 and caspase-1; the second signal leads to the assembly of the NLRP3 inflammasome, activation of caspase-1, and secretion of IL-1β (194). However, dysregulated signal transduction or excessive activation of the NLRP3 inflammasome can lead to a chronic inflammatory environment that promotes the pathogenesis and progression of various diseases, including AD (195). Activated NLRP3 inflammasomes have been observed in the brains of patients with AD and are closely associated with microglia. Study has shown that NLRP3 inflammasomes affect Aβ pathology and behavioral deficits in animal models of AD by modulating the phenotype and function of microglia (196). Notably, Aβ can also activate the NLRP3 inflammasome, leading to the release of proinflammatory cytokines such as IL-1β by microglia, contributing to neuroinflammation in AD (197). Thus, the NLRP3 inflammasome is a crucial target in AD and drugs that inhibit its activation through the inhibition of molecule formation, silencing of upstream signals, or direct/indirect inhibition of inflammasome complex formation may prove beneficial.

Inhibitors targeting the NLRP3 inflammasome have shown efficacy in suppressing neuroinflammation and hold promise as potential candidates for the prevention and treatment of AD. Among these inhibitors, dapansutrile (OLT1177) (198), a novel oral agent that selectively targets the NLRP3 inflammasome,

has demonstrated the ability to block caspase-1 activation and IL-1β maturation and release. OLT1177 is currently in clinical trials for inflammatory diseases and has been shown to be well tolerated in humans (199,200). A study using a APP/PS1 mouse model demonstrated that OLT1177 treatment can reduce microglia activation and the number of Aβ plaques in the cortex (198). An *in vitro* study also suggested that OLT1177 treatment can significantly reduce the release of pro-inflammatory cytokines and improve the inflammatory status of microglia (198). Similarly, MCC950 (201), a small molecule inhibitor specific for the NLRP3 inflammasome that contains a diarylsulfonylurea structure, has shown promise as a potential treatment for AD. MCC950 has been found to improve cognitive impairment and reduce Aβ accumulation and microglia activation in the APP/PS1 mouse model (201). An *in vitro* study has shown that MCC950 can inhibit NLRP3 inflammasome activation and IL-1β release while promoting the phagocytic effect of Aβ in microglia (201). Similar results were observed in middle-aged APPNL-F/NL-F mice, where MCC950 blocked the NLRP3 inflammasome and attenuated the reactive response of microglia induced by AβO, leading to improvements in memory impairment (202). Additionally, a lead compound, JC124 (203), based on sulfonamide-type NLRP3 inhibitors, has recently shown beneficial effects in the prevention of AD. JC124 has been found to reduce Aβ plaques and microglia activation in the brains of APP/PS1 mice and has demonstrated certain anti-inflammatory properties (203).

In addition to specific inhibitors that target the NLRP3 inflammasome, certain herbal extracts exhibit anti-inflammatory effects on this pathway. Ginkgolide B (GB) (204), a plant ester derived from *Ginkgo biloba*, has been shown to possess anti-inflammatory, antioxidant and anti-apoptotic properties, as well as potent neuroprotective effects (205,206). In an *in vitro* study, GB treatment prevented AD pathological processes and suppressed neuroinflammation in $A\beta_{1-42}$-induced BV2 microglia by inhibiting NLRP3 inflammasome activation and promoting M2 polarization (204). Paeoniflorin (PF) (207), a natural neuroprotectant from *Paeonia lactiflora* Pall, has shown significant therapeutic effects in experimental models of Parkinson's disease (208) and stroke (209). Research has shown that PF significantly reduces the protein levels of the pro-inflammatory cytokines TNF-α and IL-1β in APP/PS1 mice while increasing the anti-inflammatory cytokines IL-10 and IL-4. Its pharmacological effects are achieved by enhancing the activity of AKT, inhibiting the activation of glycogen synthase kinase-3β (GSK-3β) and NF-κB p65, and thereby reducing the NLRP3 expression levels (207).

Controlling the activity of various kinases that regulate NLRP3 inflammasome activity is another promising way to suppress neuroinflammation by inhibiting NLRP3 inflammasome activation. One such enzyme is hematopoietic cell kinase (HCK), which is involved in a number of inflammatory responses (210). It is suggested that HCK is an upstream regulator of the NLRP3 inflammasome and that the use of an HCK inhibitor [A419259 (211), a Src family kinase-specific inhibitor] can reduce NLRP3 inflammasome-mediated inflammation in microglia. Further mechanistic studies have shown that the absence of HCK and inhibition of HCK kinase activity directly affects NLRP3 function by inhibiting ASC oligomerization and inflammasome assembly. *In vivo* experiments confirm that A419259 intervention can alleviate inflammation in a mouse model of LPS-induced inflammation (211). Therefore, A419259 may therefore be a promising drug candidate for the treatment of diseases associated with NLRP3 inflammasome activation, such as AD.

Targeting the initial signal for NLRP3 inflammasome activation has emerged as an effective strategy for the treatment of neuroinflammation. TAK-242 (212), a cyclohexene derivative, is a specific small molecule inhibitor of TLR4 that is capable of crossing the BBB and exerting neuroprotective effects (213). This effect may be mediated through the modulation of the TLR4/MyD88/NF-κB/NLRP3 signaling pathway. TAK-242 can reduce TLR4 expression and attenuate inflammatory cytokine production in microglia from mice with AD carrying APP/PS1 mutations (212). As a result, there is a significant decrease in pro-inflammatory M1-type markers, such as iNOS and TNFα, while M2-type markers, including Trem-2 and Arg-1 are increased (212). Further investigation has also demonstrated that TAK-242 treatment can improve the upregulation of inflammatory cytokines, as well as MyD88, NF-κB p65 and NLRP3 (212). Similarly, the TLR4-specific inhibitor, CLI-095 (214), exerts similar anti-inflammatory effects on LPS/$A\beta_{1-42}$-induced BV-2 cells and primary microglia by ameliorating neuroinflammation through the TLR4/NLRP3 pathway (214).

Activation of the second signal of the inflammasome is a mechanism by which certain drugs, such as Pterostilbene and lignin-amides *Datura* metel seeds (LDS), can inhibit neuroinflammation. Pterostilbene, a natural compound with neuroprotective properties (215), has been found to inhibit $A\beta_{1-42}$-induced NO production, iNOS mRNA and protein expression in BV-2 cells, while also reducing the expression and secretion of inflammatory factors (216). Moreover, pterostilbene can deactivate the NLRP3/caspase-1 inflammasome activated by $A\beta_{1-42}$, demonstrating its anti-inflammatory effects. The caspase-1 inhibitor, Z-YVAD-FMK, effectively reduces $A\beta_{1-42}$-induced neuroinflammation in BV-2 cells, providing further support for this hypothesis (216). In addition to pterostilbene, LDS is also able to ameliorate neuroinflammation through the NLRP3/caspase-1 pathway. Wang *et al* (217) found that LDS had anti-inflammatory activity in LPS-induced BV2 cells. Additionally, PPSR (PEG-PEI/siROCK2), a synthetic molecule used in gene therapy for AD, was found to inhibit the increase in IL-1β induced by LPS/Aβ in primary microglia through the NLRP3/caspase-1 pathway, thus exhibiting anti-inflammatory effects (218). However, the specific mechanism through which PPSR regulates the NLRP3/caspase-1 pathway remains to be elucidated and requires further investigation (219).

Gasdermin D (GSDMD) plays a crucial role in pyroptosis, whereby intracellular inflammasomes trigger caspase-1-mediated cleavage of the effector protein GSDMD to form p30-GSDMD, resulting in the formation of cell membrane pores and release the inflammatory factors (220). Recently, two novel GSDMD cleavage inhibitors, Sulfa-4 and Sulfa-22 (221), were shown to effectively attenuate neuroinflammation and prevent AD by disrupting the NLRP3/caspase-1/GSDMD classical pyroptosis pathway. The investigation demonstrated that the administration of Sulfa-4 and Sulfa-22 inhibited the activation of microglia in the brains of APP/PS1 mice, reduced

the expression of inflammatory factors and suppressed the production of p30-GSDMD and upstream NLRP3 inflammasome and caspase-1 proteins. Furthermore, the study revealed the specific binding relationship between Sulfa-4 and Sulfa-22 and the GSDMD protein, establishing a valuable basis for the development of drugs to target neuroinflammation in AD (221).

Donepezil is a commonly used AChE inhibitor for the treatment of AD (222). There is evidence that cognitive function, activities of daily living and overall clinical status, as assessed by healthcare professionals, improve slightly in individuals with AD who are treated with donepezil. In addition, the use of donepezil does not appear to significantly increase or decrease healthcare costs compared with placebo. However, it is important to note that withdrawal rates and adverse events tended to be higher at higher doses (223,224). Recent study has demonstrated that donepezil can effectively inhibit LPS-induced neuroinflammation by downregulating the mRNA levels of proinflammatory cytokines in BV2 cells (225). This effect can be attributed to the intervention of the MAPK/NLRP3/STAT3 pathway. Furthermore, in LPS-treated wild-type mice, treatment with donepezil effectively reduced the activation and quantity of microglia, as well as the levels of proinflammatory cytokines (225). In addition, donepezil was also found to improve the neuroinflammation induced by Aβ stimulation in 5XFAD mice (225). These findings are supported by the study by Kim *et al* (226), which demonstrated that Donepezil directly inhibits AβO-induced microglia activation by blocking the MAPK and NF-κB signals, thereby improving neuroinflammation and mitigating memory impairment.

AMPK is a vital molecule that plays a critical role in regulating energy metabolism and mitochondrial function (226). Mitochondrial dynamics are primarily controlled by mitosis (227), which promotes the expression of phosphate and tensin homolog deleted on chromosome 10 (PTEN)-induced kinase 1 (PINK1) on the damaged outer mitochondrial membrane. This, in turn, elevates the activity of the E3 ubiquitin ligase Parkin, modulating the autophagic process (228). Tetrahydroxy stilbene glycoside (TSG) (229), the major bioactive component of traditional Chinese medicine Polygoni multiflori Radix, exhibits potent antioxidant and anti-atherosclerotic properties (230) and has demonstrated a neuroprotective in repairing brain injury (231). A recent study has found that TSG can attenuate the LPS-induced inflammatory response in microglia by inhibiting the NLRP3 signaling pathway while promoting the autophagic process mediated by the AMPK/PINK1/Parkin pathway (229). Notably, the neuroprotective effect of TSG is abolished in PINK1 or Parkin knockout models, underscoring the critical role of inhibition of NLRP3 activation through the AMPK/PINK1/Parkin signaling pathway for TSG to exert its neuroprotective effects (229).

In addition, RhoA, a member of the Rho family of GTPases, forms the RhoA/ROCK signaling pathway with the downstream effector Rho-dependent coiled-coil kinase (ROCK) (232). Activation of this pathway can further activate NLRP3, leading to neuroinflammation (233) and increased Aβ production (234) through APP cleavage-dependent secretion, contributing to Aβ-induced neurotoxicity. The RhoA/ROCK signaling pathway also affects the phagocytic function (235) of microglia and neuroinflammatory responses (236), as well as interactions with Aβ and microglia (237). A recent study has demonstrated that small molecule inhibitors, such as Fasudil and Y27632, can alleviate AD pathogenesis by suppressing the RhoA/ROCK/NLRP3 signaling pathway, thereby reducing LPS-induced inflammatory responses (238).

In summary, targeting the NLRP3 inflammasome has the potential to provide a multitude of effective therapeutic avenues for managing neuroinflammation in AD (Fig. 3 and Table III).

## 4. PPAR

Peroxisome proliferator-activated receptors (PPARs) comprise three distinct forms, including PPARα, PPARβ/δ and PPARγ (239), with a large body of literature focusing on PPARγ (240-243). These receptors play a significant role in regulating energy homeostasis and metabolism (244) throughout the body (245). In the brain, PPARs are widely distributed in cognitive centers such as the prefrontal cortex and hippocampus, which are vulnerable to neurodegeneration in AD (246). Despite low baseline expression of PPARγ in the brain, it has been observed to increase in response to AD pathology (247). Studies have shown that PPARγ agonists not only improve cognitive function in patients with AD and animal models (248,249), but also reduce Aβ levels (250). Furthermore, PPARγ is highly expressed in microglia (251) and its activation induces microglia to adopt an anti-inflammatory phenotype, thereby suppressing neuroinflammatory responses (252,253). These findings highlight PPARγ as an attractive therapeutic target for the treatment of AD, with the potential to ameliorate disease pathology.

Current research has demonstrated the anti-inflammatory effects of PPARγ agonists, particularly pioglitazone (PIO), in various mouse models of AD. Berberine (BBR), an alkaloid extracted from Coptidis Rhizoma (254) with similar binding affinity to the PPARγ protein as PIO, has potentially overlapping effects (255). BBR has been found to partially improve neuroinflammation by reducing IL-6 and TNF-α levels in LPS-induced BV-2 cells, indicating a potential preventive or delayed onset of early AD (255). Rice bran extract (RBE), a novel PPARγ regulator that enhances cognitive function in rats (256), also exerts anti-inflammatory effects by regulating microglia phenotype in LPS-induced mice (257). RBE and PIO can both regulate microglia M1 to M2 phenotype, significantly reducing the expression of NF-κB and pro-inflammatory microglia markers (CD45), while increasing the expression of anti-inflammatory microglia markers and PPARγ (257). Additionally, RBE can reduce $A\beta_{42}$ deposition and p-tau protein levels, thereby effectively ameliorating AD pathology (257).

AD is known to be closely associated with the activation of inflammation, which can be exacerbated by obesity and exacerbate cognitive impairment (258). *Malva parviflora* extract (MpHE), with its hypoglycemic, anti-inflammatory and antioxidant properties (258,259), has demonstrated the ability to improve the adverse effects of a high-fat diet in an AD mouse model through a PPARγ-dependent mechanism. MpHE not only improved spatial learning deficits and reduced insoluble Aβ peptides in the hippocampus of lean and obese 5XFAD mice but also inhibited the accumulation of small glial cells around Aβ plaques and the conversion to a pro-inflammatory

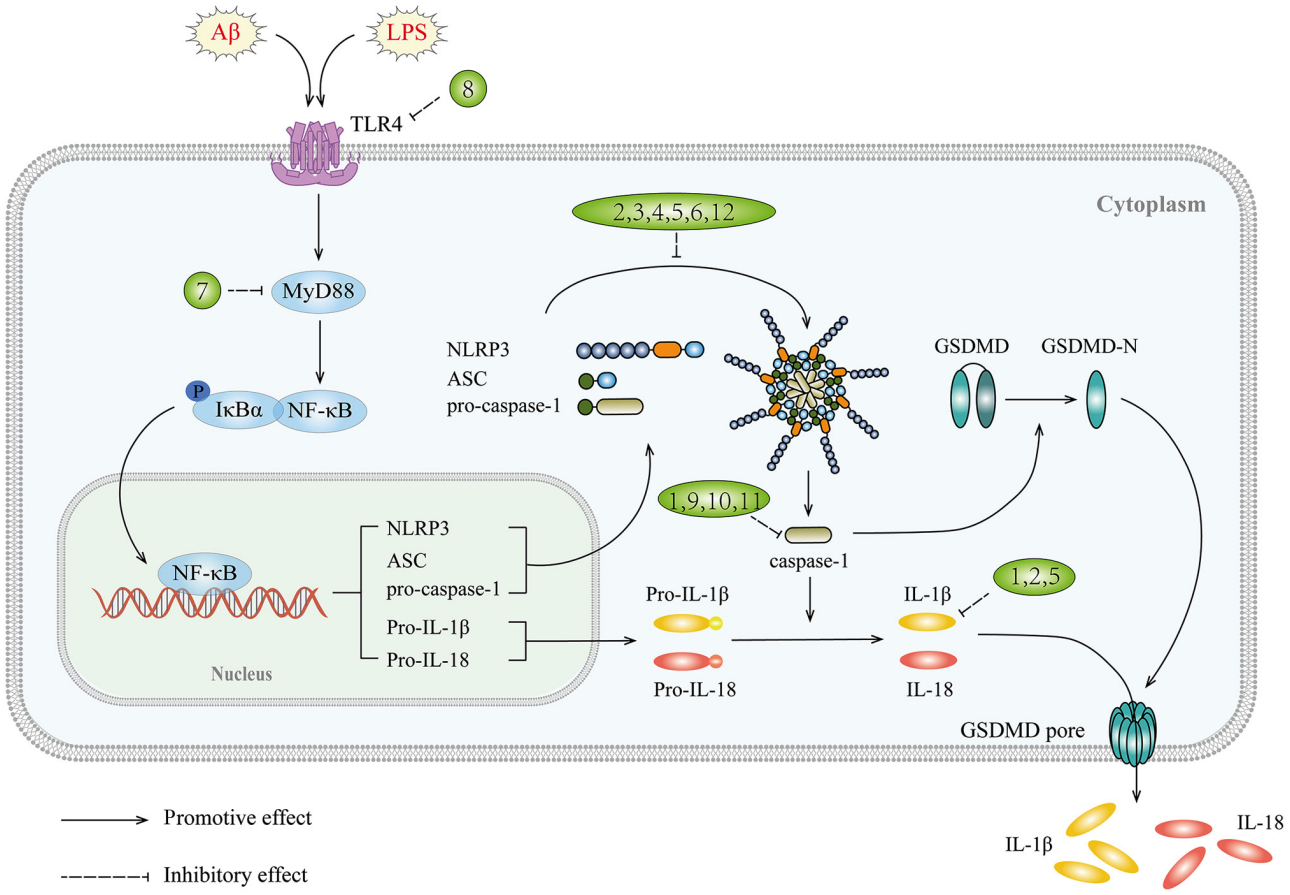


Figure 3. NLRP3 signaling pathway and targets of inhibitors against neuroinflammation in AD. NLRP3, NOD-like receptor thermal protein domain associated protein 3; AD, Alzheimer's disease; 1, dapansutrile; 2, JC124; 3, MCC950; 4, ginkgolide B; 5, paeoniflorin; 6, A419259; 7, TAK-242; 8, CLI-095; 9, PEG-PEI/short interfering ROCK2; 10, pterostilbene; 11, LDS; 12, sulfa-4 and sulfa-22; Aβ, amyloid β; LPS, lipopolysaccharide; TLRs, Toll-like receptors; MyD88, myeloid differentiation factor 88.

M1 phenotype while promoting phagocytic capacity (260). Rescue of the phagocytic capacity of microglial cells by MpHE was achieved through a PPARγ/CD36-dependent mechanism (260). Angiotensin II receptor blockers (ARBs), used to treat metabolic disorders, have been found to ameliorate inflammation in several brain disorders by blocking angiotensin II type 1 receptors and activating PPARγ, thus exerting a neuroprotective effect (261,262). Clinical trials have shown that ARBs have a positive effect on cognitive decline (263). In addition, it has been shown that telmisartan, a typical ARB, can ameliorate AβO-induced inflammation in microglia (264). Telmisartan (264) has been shown to decrease the expression of the pro-inflammatory cytokine IL-1β, while increasing the expression of PTEN, a key lipid and protein phosphatase, and the anti-inflammatory cytokine IL-10. Furthermore, Telmisartan has also been shown to inhibit the activity of NF-κB, a key transcription factor involved in inflammation and its upstream regulators Akt and ERK (264). These anti-inflammatory effects of telmisartan have been found to be PPARγ dependent, with the PPARγ inhibitor GW9662 blocking the expression of PTEN (264). Taken together, telmisartan ameliorates AβO-induced microglial inflammation via the PPARγ/PTEN pathways. Other compounds with potential therapeutic benefit in AD through anti-inflammatory mechanisms include Bis (ethylmaltolato) oxidovanadium (BEOV) and platycodigenin. BEOV (265) has demonstrated the ability to reduce levels of pro-inflammatory cytokines and interfere with NF-κB signaling in Aβ-stimulated BV2 microglia and the hippocampus of APP/PS1 mice, and its effects have been found to be PPARγ dependent. Platycodigenin (266), a triterpenoid compound found mainly in *Platycodon grandifloras*, demonstrates neuroprotective and anti-inflammatory activity. Study reveals that platycodigenin can inhibit the secretion of pro-inflammatory cytokines in Aβ-stimulated BV-2 microglia and induce M1-type microglia to polarize towards the M2 type (266). Their anti-neuroinflammatory effects have been attributed to the inhibition of p38 MAPK and NF-κB p65 signaling while activating PPARγ. Although PPAR-γ agonists have shown promising anti-inflammatory activity and their potential use in the treatment of AD, long-term use of these drugs often results in serious side effects, including congestive heart failure, oedema, and weight gain (267,268). Therefore, there is an urgent need to develop PPARγ-targeting drugs with improved tolerability (Fig. 4 and Table IV).

## 5. STAT3

STATs are a group of potential transcription factors that are activated by cytokines and growth factors. When stimulated by LPS, IFN-γ, and other cytokines, they can trigger inflammatory signals that translocate STATs from the cytoplasm to the nucleus and activate the expression of a number of pro-inflammatory

Table III. Drugs that prevent and treat AD through the NLRP3 signaling pathway.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Lonnemann *et al*, 2020 | OLT1177/- | APP/PS1Δ E9 mice | LPS-induced primary microglia | *In vivo:* 3.75, 7.5 g/kg; 3 months *In vitro:* 5, 10 $\mu$M; 24 h | ↓: CD68, TNF-α, IL-1β, IL-6, NLRP3, Iba-1, the number of plaques | NLRP3 | (198) |
| Dempsey *et al*, 2017 | MCC950/- | APP/PS1 double transgenic AD mice | LPS+Aβ-induced primary microglia | *In vivo:* 10 mg/kg; 3 months *In vitro:* 100 nM; 5 h | ↓: IL-1β, LDH, caspase 1, inflammasome assembly, Aβ, CD11b, CD68 | NLRP3 | (201) |
| Fekete *et al*, 2019 | | AβO-induced AD rats APPNL-F/NL-F mice | - | *In vivo:* 1 $\mu$g; 4 weeks | ↓:Iba1, Cd11b, Cd68, Cd80, Cd86, RT1-EC2, Ccl2, Cxcl10, C3, Cfb, NLR3, Il1b, Tnf, Il12b, Nos2, Cx3cl1, Cd200, Cd22, Cx3cr1, Cd200r, Cd45 ↑: Scn1,IL-10 | - | (202) |
| Kuwar *et al*, 2021 | JC124/- | APP/PS1 double transgenic mice with AD | - | *In vivo:* 50, 100 mg/kg; 3 months | ↓: Aβ, Iba1, HMGB1, GFAP, D1 ↑: generation and survival of new neurons, pre-synaptic proteins, synapsin-1, synaptophysin | NLRP3 | (203) |
| Zhang *et al*, 2021 | GB/*Ginkgo biloba* | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 100 $\mu$M; 2 h | ↓: Cytotoxic, NLRP3, caspase-1, IL-1β, Aβ, CD16/32, iNOS ↑:CD206, Arg-1, CD206 | NLRP3 | (204) |
| Zhang *et al*, 2015 | PF/*Paeonia lactiflora* Pall | APP/PS1 double transgenic mice with AD | - | *In vivo:* 5 mg/kg; 4 weeks | ↓: Aβ, GFAP, CD11b, TNF-α, IL-1β, p-NF-κB p65, p-I-κBa, NLRP3, caspase-1 p20 ↑: IL-10, IL-4, p-AKT, p-GSK3β-pSer9 | NLRP3 | (207) |
| Kong *et al*, 2020 | A419259/- | LPS-induced C57BL/6J mice | LPS-induced primary microglia | *In vivo:* 30 mg/kg; 3 h *In vitro:* 1 $\mu$M; 1 h | ↓: Caspase 1, IL-1β, ASC, the interaction between HCK and NLRP3, IL-6, IL-10 | NLRP3 | (211) |

Table III. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Cui *et al*, 2020 | TAK-242/- | APP/PS1 double transgenic mice with AD | Aβ-induced BV2 cells | *In vivo:* 2 mg/kg; 28 days *In vitro:* 100 nM; 8 h | ↓: TLR4, CD11b, amoeboid microglial cells, iNOS, TNFα, MyD88, NF-κB p65, NLRP3, Bax, iNOS ↑: TREM-2,Arg-1 | TLR4/MyD88/NF-κB/NLRP3 | (212) |
| Liu *et al*, 2020 | CLI-095/- | - | LPS + $A\beta_{1-42}$-induced BV2 cells and primary microglia | *In vitro:* 1 $\mu$M; 2 h | ↓: NLRP3, ASC, caspase1 p10, IL-1β, Iba-1, IL-1β, TNF-α, iNOS, Cox-2 | TLR4/NLRP3 | (214) |
| Li *et al*, 2018 | Pterostilbene/- | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 5, 10 $\mu$M; 24 h | ↓: NO, iNOS, IL-6, IL-1β, TNF-α, NLRP3, caspase1 | NLRP3/caspase1 | (216) |
| Wang *et al*, 2021 | LDS/- | - | LPS-induced BV2 cells | *In vitro:* 400, 200, 100 $\mu$g/ml; 12 h | ↓: iNOS, COX-2, NO, IL-1β, TNFα, IL-6, NLRP3, TLR4, MyD88, caspase1, Iba1, Tau | NLRP3/caspase1 | (217) |
| Liu *et al*, 2022 | PPSR/- | - | LPS+$A\beta_{42}$-induced primary microglia | *In vitro:* transfection; 6 h | ↓: ROCK2, IL-1β, NLRP3, pro-caspase-1, caspase-1 | NLRP3/caspase1 | (219) |
| Han *et al*, 2021 | Sulfa-4 and sulfa-22/- | APP/PS1 double transgenic mice with AD | LPS+nigericin-induced BV2 cells | *In vivo:* 5 mg/kg; 14 days *In vitro:* Sulfa-4 ($IC_{50}$ of 3 $\mu$M); 4 h Sulfa-22 ($IC_{50}$ of 5 $\mu$M); 4 h | ↓: LDH, PI uptake rate, p30-GSDMD, IL-18, IL-1β, TNF-α, NLRP3, Caspase-1, IBA-1, CD11c | NLRP3/caspase1/GSDMD | (221) |
| Kim *et al*, 2021 | Donepezil/- | LPS-induced C57BL6/J mice 5XFAD mice APP/PS1 double transgenic mice with AD | LPS-induced BV2 cells | *In vivo:* 1 mpk; 3 days/2 weeks *In vitro:* 50 $\mu$M; 23.5 h | ↓: COX-2, IL-1β, IL-6, iNOS, ROS, p-AKTser473, p-AKTT308, p-ERK, p-P38 T180/Y18, p-NF-kBSer536, p-STAT3 Ser727, NLRP3, pro-IL-1β, IL-1β, Iba-1,GFAP | MAPK/NLRP3/STAT3 | (225) |

Table III. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Kim *et al*, 2014 | | AβO-induced mice with AD | $AβO_{1-42}$-induced BV2 cells, rat primary microglia and primary hippocampal cells | *In vivo:* 2 mg/kg; 5 days *In vitro:* 0.1, 1 $\mu$M; 24 h | ↓: NO, TNF-α, IL-1β, PGE2, iNOS, COX-2, p38 MAPK, NF-κB p65 translocation to nucleus, Mac-1, GFAP ↑:cell viability | MAPK and NF-κB signaling | (226) |
| Gao *et al*, 2020 | TSG/ Polygoni multiflori Radix | - | LPS-induced BV2 cells | *In vitro:* 1, 10 $\mu$M; 10, 100 nM; 24 h | ↓: TNF-α, IL-1β, IL-18, iNOS, COX-2, P62, p-Drp1(S637), MFF, NLRP3, pro-caspase-1, cleaved caspase-1, IL-1β/IL-1F2, IL-3, G-CSF, GM-CSF, IL-5, CCL5/RANTES, CCL4/MIP1β, IL-2, IL-4, IL-10, IFN-γ, CCL5/RANTES, CCL4/MIP1β, IL-2 ↑: LC3-II/LC3-I, Parkin, PINK1, Beclin1, Drp1, Mfn2 | AMPK related PINK1/ Parkin/ NLRP3 | (229) |
| Zhang *et al*, 2019 | Fasudil and Y27632/- | - | LPS-induced BV2 cells | *In vitro:* Fasudil (50 $\mu$M), Y27632 (10 $\mu$M); 24 h | ↓: Cell migration, NLRP3, pro-CASP1, pro-IL-1β,IL-1β | RhoA/ ROCK/ NLRP3 | (238) |

AD, Alzheimer's disease; OLT1177, dapansutrile; GB, ginkgolide B; PF, paeoniflorin; TAK-242, ethyl (6R)-6-[N-(2-chloro-4-fluorophenyl) sulfamoyl] cyclohex-1-ene-1-carboxylate); LDS, lignin-amides from Datura metel seeds; PPSR, PEG-PEI/siROCK2; TSG, tetrahydroxy stilbene glycoside; Aβ, amyloid β; APP/PS1, amyloid-β protein/presenilin-1; 5XFAD, 5X familial Alzheimer's disease; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; ASC, apoptosis-associated speck-like protein; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; GSDMD, gasdermin D; HCK, Hematopoietic cell kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; LPS, lipopolysaccharide; MyD88, myeloid differentiation factor 88; MAPK, mitogen-activated protein kinase; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; ROCK, Rho-dependent coiled-coil kinase; TLRs, Toll-like receptors; p-phosphorylated; NF-κB, nuclear factor-kappa-B; Iba-1, ionized calcium binding adaptor molecule 1; STAT3, signal transducers and activators of transcription 3; AP-1, activator protein 1; PGE2, prostaglandin E2.

genes (269). Of the seven types of STAT proteins found in humans, STAT3 has been extensively studied for its involvement in acute stress responses, cell growth, differentiation, and immune reactions (270). Previous studies have demonstrated elevated activation of STAT3 in hippocampal slices in patients with AD (271) and mouse models (272). Furthermore, STAT3 plays a crucial role in regulating the reactivity of microglia and in mediating pro-inflammatory responses, indicating a close functional interplay with microglia (273). Given the dependence of neuronal differentiation and cytokine signaling on STAT3, STAT3 phosphorylation is closely linked to cytokine secretion (274). Therefore, targeting the signal network that activates STAT3 may be an effective therapeutic strategy for the treatment of AD (275).

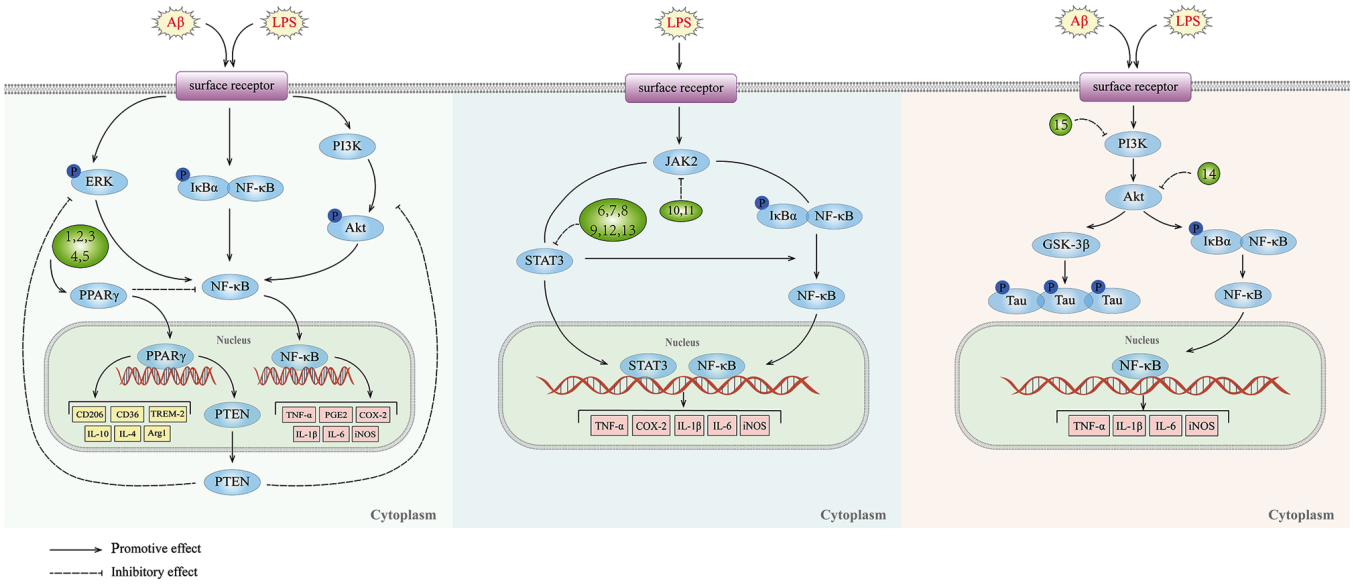


Figure 4. PPAR, STAT3 and PI3K/Akt signaling pathways and targets of inhibitors against neuroinflammation in AD. PPAR, peroxisome proliferator-activated receptor; AD, Alzheimer's disease; 1, berberine; 2, rice bran extract; 3, telmisartan; 4, bis(ethylmaltolato)oxidovanadium; 5, platycodigenin; 6, (E)-2, 4-bis(p-hydroxyphenyl)-2-butenal; 7, (E)-2-methoxy-4-(3-(4-methoxyphenyl) prop-1-en-1-yl) phenol; 8, astaxanthin; 9, stattic; 10, protosappanin A; 11, curcumin; 12, Ent-Sauchinone; 13, sorafenib; 14, DHCR24 (3-β-hydroxysteroid-Δ-24-reductase); 15, sulforaphene; Aβ, amyloid β; LPS, lipopolysaccharide; IKK, IκB kinase; JAK2, Janus kinase; GSK-3β, glycogen synthase kinase-3β; PTEN, phosphate and tensin homolog deleted on chromosome 10.

It has been reported that (E)-2, 4-bis (p-hydroxyphenyl)-2-butenal (HPB242) (276) exhibits significant anti-inflammatory effects by inhibiting STAT3 activation in AD. Another structurally similar compound, (E)-2-methoxy-4-(3-(4-methoxyphenyl) prop-1-en-1-yl) phenol (MMPP) (277), has been found to inhibit LPS-induced neuroinflammation and memory impairment. In a mouse model of neuroinflammation induced by intraperitoneal injection of LPS, MMPP significantly reduced Aβ deposition in the brain and improved cognitive dysfunction by inhibiting COX-2 and iNOS expression, as well as the activation of microglia in the brain. Furthermore, MMPP treatment reduces the expression of inflammatory protein and APP in LPS-induced BV-2 microglia. In both *in vivo* and *in vitro* experiments, MMPP can inhibit the DNA binding activity of STAT3 activation (277). Additionally, axstaxanthin (AXT), a naturally occurring carotenoid compound with anti-inflammatory, antioxidant and neuroprotective properties (278), has exhibited effects on MMPP. *In vivo* and *in vitro* experiments have shown that AXT reduces the expression of inflammatory proteins induced by LPS and improves LPS-induced memory impairment by directly binding to the DNA binding domain (DBD) and linker domain (LD) of STAT3, resulting in an anti-neuroinflammatory response and inhibiting APP formation (279).

BACE1 plays a critical role in in the generation of Aβ (280), a major component of AD pathology. The transcriptional regulation of BACE1 by STAT3 (271) is strongly implicated in AD pathology as it can elevate Aβ production (281). Notably, STAT3 is activated in response to LPS-induced neuroinflammation, which in turn increases BACE1 levels in the brain (275). Treatment with stattic, a selective inhibitor of STAT3 activation, has been shown to prevent neuroinflammation and abnormal BACE1 regulation (282). In an LPS-induced mouse model of neuroinflammation, stattic could inhibit STAT3 phosphorylation and microglia activation in the hippocampus, consequently reducing levels of inflammatory factors in the brain. Notably, treatment with both LPS and Stattic significantly reduced hippocampal BACE1 levels in the hippocampus compared to LPS alone (282). These findings suggest that Stattic may address two pathological aspects of AD in the hippocampus, making it a promising candidate for the treatment of AD.

Janus kinase 2 (JAK2) is a non-receptor protein tyrosine kinase that plays a critical role in the JAK2/STAT3 signaling pathway in the CNS (283). Activation of the JAK2/STAT3 pathway leads to the transcription and expression of inflammatory genes, resulting in an excessive accumulation of inflammatory mediators and subsequent inflammation (284). Therefore, inhibition of the JAK2/STAT3 pathway may be a potential therapeutic approach for neuroinflammatory injury. A promising compound, protosappanin A (PTA), which is a major bioactive component isolated from *Caesalpinia sappan* L., was found to regulate LPS-induced neuroinflammation by inhibiting the JAK2/STAT3 pathway (285). In the LPS-induced BV2 cell model, PTA treatment reduced the production of TNF-α, IL-1β and NO in microglia, while also dose-dependently decreasing IL-6 and IL-1β mRNA expression (285). A further study demonstrated that PTA inhibited JAK2/STAT3-dependent inflammatory pathways by downregulating JAK2 and STAT3 phosphorylation as well as STAT3 nuclear translocation (285). Furthermore, the Porro *et al* (286) found that curcumin, a pigment isolated from *Curcuma longa* (turmeric) with anti-inflammatory, antioxidant, and anticancer activities (287), regulates neuroinflammation by inducing an anti-inflammatory response against microglia through the JAK2/STAT/SOCS (suppressor of cytokine signaling) signaling pathway. Curcumin treatment increased the production of the anti-inflammatory cytokines IL-4 and

Table IV. Drugs that prevent and treat Alzheimer's disease through other signaling pathways.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Wong *et al*, 2021 | Berberine/ Coptidis Rhizoma | - | LPS-induced BV2 cells | *In vitro:* 0.3-10 $\mu$M; 2 h | ↓: Basal respiration, TNF-α, IL-6 | PPARγ | (255) |
| El-Din *et al*, 2021 | Rice bran extract/rice bran | LPS-induced Swiss Albino mice | - | *In vivo*: 100 mg/kg; 3 weeks | ↓: CD45, Aβ-42, p-Tau, NF-κB, neuron ↑: arginase1, CD36, CD163 | PPARγ | (257) |
| Medrano-Jiménez *et al*, 2019 | *Malva parviflora* hydroalcoholic leaf extract/ *Malva parviflora* | 5XFAD mice LPS-induced CD1 mice | - | *In vivo:* 50 mg/kg; 8 months 25, 50, 100 mg/kg; 7 days | ↓: Aβ, CD86, TNF, IL-6 ↑: phagocytic activity, microglia accumulation around the Aβ plaques, Mgl1, TREM-2, PPAR-γ, CD36 | PPARγ/ CD36 | (260) |
| Wang *et al*, 2020 | telmisartan/- | - | AβO-induced BV2 cells | *In vitro:* 5 $\mu$M-2 h | ↓: IL-1β, TNF-α, NF-κB activation, p-Akt, p-ERK ↑: IL-10, PPARγ, PTEN | PPARγ/ PTEN pathway | (264) |
| He *et al*, 2021 | Bis (ethylmaltolato) oxidovanadium | APP/ PS1 double transgenic mice with AD | Aβ-induced BV2 cells | *In vivo:* 0.2, 1 mM; 3 months *In vitro:* 5, 10, 20 $\mu$mol/l; 2 h | ↓: NO, PGE2, iNOS, COX-2, TNF-α, I L-6, IL-1β, p-IκB-α, NF-κB/p65 translocation, Iba1, iNOS, COX-2 ↑: PPARγ | PPARγ/ NF-κB | (265) |
| Yang *et al*, 2019 | Platycodigenin/*Platycodon grandiflora*s | - | Aβ-induced BV2 cells | *In vitro:* 0.1, 1, 10 $\mu$M; 12 h | ↓: TNF-α, IL-1β, IL-6, NO, iNOS, Cox2, p- p65, p38, neuronal death, neuritic atrophy ↑: IL-10, IL4, CD206, Arg1, TGFβ, Ym1/2, PPARγ | PPARγ | (266) |
| Jin *et al*, 2013 | (E)-2, 4-bis (p-hydroxyphenyl)-2-butenal | Tg2576 mice | - | *In vivo:* 5 mg/kg; 1 month | ↓: Aβ plaques, Aβ1-42, β-secretase, APP, C99, BACE1, GFAP, Iba1, iNOS, COX-2, NF-κB translocation, DNA binding activity of NF-κB, p-IκB, p-STAT1, p-STAT3 | STAT3 | (276) |

Table IV. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Choi *et al*, 2017 | (E)-2-methoxy-4-(3-(4-methoxyphenyl) prop-1-en-1-yl) phenol | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 5 mg/kg; 4 weeks *In vitro:* 1, 5, 10 $\mu$g/ml; 24 h | ↓: Aβ, β-secretase, APP, BACE1, C99, GFAP, the DNA binding activity of STAT3, p-STAT3, Iba-1, iNOS, COX-2, IL-6, IL-10 | STAT3 | (277) |
| Han *et al*, 2019 | Astaxanthin/ marine environment | LPS-induced ICR mice | LPS-induced BV2 cells | *In vivo:* 30, 50 mg/kg; 4 weeks *In vitro:* 5, 10, 20 $\mu$M; 24 h | ↓: Aβ, β-secretase, APP, BACE1, GFAP, IBA-1, iNOS, COX-2, MCP-1, MIP-1α, MIP-1β, GSH/GSSG, total GSH, NO, TBARS, STAT3 activation | STAT3 | (279) |
| Millot *et al*, 2020 | Stattic/- | LPS-induced C57BL/6 mice | - | *In vivo:* 20 mg/kg; 3 days | ↓: PhosphoSTAT3Tyr 705/STAT3 ratio, IBA-1, MAC-1, IL-1β, TNF-α, IL-6, IFN-γ, BACE1 | STAT3 | (282) |
| Wang *et al*, 2017 | Protosappanin A/ *Caesalpinia sappan* L. | - | LPS-induced BV2 cells | *In vitro:* 12.5, 25, 50 $\mu$mol·l$^{-1}$; 24 h | ↓: NO, TNF-α, IL-1β, IL-6, MCP-1, p-JAK2, p-STAT3, STAT3 translocation | JAK2/ STAT3 | (285) |
| Porro *et al*, 2019 | Curcumin/ *Curcuma longa* (turmeric) | - | LPS-induced BV2 cells | *In vitro:* 10, 30, 50 $\mu$M; 1 h | ↓: p-JAK2, p-STAT3, iNOS ↑: IL-4, IL-10, SOCS-1, ARG-1 | JAK/ STAT3/ SOCS | (286) |
| Song *et al*, 2014 | Ent-Sauchinone/plants | - | LPS-induced BV2 cells | *In vitro:* 1, 5, 10 $\mu$M; 24 h | ↓: iNOS,COX-2, ROS, NF-κB binding activity, p-IκB, NF-κB translocation, BACE1, C99, I ba1, Aβ accumulation, DNA binding activity of STAT3, STAT3 activity | STAT3/ NF-κB | (290) |
| Kim *et al*, 2021 | Sorafenib/- | LPS induced C57BL 6/J mice 5XFAD mice | LPS-induced BV2 cells | *In vivo:* 10 mg/kg; 3 times at 2-h intervals 10 mg/kg; 3 days *In vitro:* 5 $\mu$M; 30 min | ↓: COX-2, IL-1β, p-AKTS473, p-P38T 180/Y182, p-STAT 3S727, p-NF-kB S536, caspase-3, Iba-1, GFAP, p-AKT, shank-1 | AKT/ P38-linked STAT3/ NF-κB | (291) |

Table IV. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Zu *et al*, 2020 | DHCR24 (3-β-hydroxysteroid-Δ-24-reductase)/- | - | $A\beta_{25-35}$-induced BV2 cells | *In vitro:* lentiviral transfection-72 h | ↓: iNOS, iNOSCD 11b, IL-1β, TNF-α ↑: Arg-1CD11b, IL-4, TGF-β, p-Akt, p-GSK3β(S9), p-Akt/Akt, p-GSK3β/GSK 3β | Akt/GSK -3β | (298) |
| Yang *et al*, 2020 | Sulforaphene/ Raphani Semen | STZ-induced SD rats | LPS-induced BV2 cells | *In vivo:* 25, 50 mg/kg; 6 weeks *In vitro:* 0.5-32 $\mu$M; 1 h | ↓: TNF-α, IL-6, Iba-1, GFAP, p-tau (Thr205), p-tau (Ser396), p-tau (Ser404), NO, IL-1β, NF-κB p65 translocation ↑: IL-10, p-Akt/Akt, p-GSK-3β (S9)/GSK-3β,PI3K p110α | PI3K/ Akt/GSK-3 β | (300) |
| Zhang *et al*, 2013 | Sildenafil/- | APP/ PS1 double transgenic mice with AD | - | *In vivo:* 10 mg/kg; 10 days | ↓: IL-1β, IL-6, TNF-α, Aβ1-40, Aβ1-42 ↑: pCREB | PKG/ CREB | (313) |
| Wang *et al*, 2022 | Thioperamide/- | LPS-induced C57BL/ 6 mice | LPS-induced BV2 cells | *In vivo:* 5 mg/kg; 7 days *In vitro:* 1 $\mu$M; 30 min | ↓: Iba-1, IL-1β, IL-6, TNF-α, NF-κB/CBP ↑: BrdU, DCX, BrdU/DCX, BrdU/ NeuN, p-CREB, p-PKA, CREB/CBP, IL-4, IL-10, BDNF, total dendritic length | histamine-dependent H2R/ cAMP/ PKA/ CREB | (317) |
| Fragoulis *et al*, 2017 | Methysticin/ kava | APP/ PS1 double transgenic mice with AD | - | *In vivo:* 6 mg/kg; 3 weeks | ↓: Iba1, GFAP, TNF-α, IL-17A ↑: Nrf2/ARE, HO-1, Gclc, Nrf2 | Nrf2 | (323) |
| Mattioli *et al*, 2019 | Polyphenol extract/Arabidopsis thaliana | transgenic AD flies | $A\beta_{25-35}$-induced BV2 cells | *In vivo:* 40 $\mu$l/ml; 3-5 days, 10-12 days *In vitro:* 20 $\mu$l/ml; 24 h | ↓: IL-6, IL-1β, TNF-α, p65 ↑: IL-4, IL-10, IL-13, Nrf2, HO-1, NQO1 | Nrf2 | (325) |
| Alvariño *et al*, 2019 | Gracilin A/ *Spongionella gracilis* | - | LPS-induced BV2 cells | *In vitro:* 0.01-1 $\mu$M; 1 h | ↓: IL-1β, IL-6, TNF-α, GM-CSF, ROS, NO, iNOS, p38 MAPK kinase, p-p38, p65 ↑: Nrf2 | Nrf2 | (327) |

Table IV. Continued.

| First author, year | Compound and original source | *In vivo* model | *In vitro* model | Dose and drug administration time | Targets | Signaling pathways | (Refs.) |
|---|---|---|---|---|---|---|---|
| Huang *et al*, 2020 | Engeletin/ *Engelhardia roxburghiana* | - | $A\beta_{1-42}$-induced BV2 cells | *In vitro:* 20, 40 $\mu$M; 24 h | ↓: ROS, MDA, LDH, NO, iNOS, TNF-α, IL-1β, IL-6, Keap1 cell viability ↑: GSH-Px, SOD, Nrf2 | Keap1/ Nrf2 | (331) |
| Eom *et al*, 2012 | Bambusae Caulis in Taeniam ethyl acetate fraction/ *Phyllostachys nigra* var. *henonis* | - | LPS-induced BV2 cells | *In vitro:* 10, 20, 40, 60, 80 $\mu$g/ml; 1 h | ↓: NO, TNF-α, IL-1β, IL-6, iNOS, COX-2 ↑: HO-1, Nrf2 | Nrf2/ HO-1 | (334) |
| Chen *et al*, 2017 | L-F001/- | LPS-induced C57BL/ 6 mice | LPS-induced BV2 cells | *In vivo:* 35 mg/kg; 24 h *In vitro:* 0-10 $\mu$M; 24 h | ↓: Reactive oxygen, NO, IL-6, TNF-α, CD16/32, iNOS, COX-2, NF-κB p65, degradation of IκB ↑: CD206,Nrf2 | Nrf2 and NF-κB | (335) |
| Gao *et al*, 2020 | Beta-naphthoflavone | - | LPS-induced BV2 cells | *In vitro:* 2.5, 5, 10, 20 $\mu$M; 0, 0.5, 1, 3, 6 h | ↓: IL-6, TNF-α, iNOS, COX-2, deterioration of IκBα, p-IκB, p-p65, NF-κB p65 translocation ↑: activation of AKT, Nrf2 translocation, HO-1 | Akt/ Nrf-2/HO-1 signaling axis | (338) |
| Jin *et al*, 2021 | Cangrelor/- | $A\beta_{1-42}$-induced mice with AD | - | *In vivo:* 2, 4 $\mu$g/mouse; 6 days | ↓: GPR17, BACE1, Aβ1-42, MDA, TNF-α, IL-1β, Iba1, NF-κB p65 ↑: GSH, SOD, CAT, Nrf2, HO-1, PSD-95, SYN | Nrf2/ HO-1 and NF-κB | (337) |
| Park *et al*, 2018 | Bakkenolide B/ *Petasites japonicus* | - | LPS-induced BV2 cells | *In vitro:* 40 $\mu$M-4,8, 12,16,24 h | ↓: IL-1β, IL-6, IL-12, TNF-α, ROS ↑: Nrf2, HO-1, NQO1, ARE-promoter activity, p-AMPK | AMPK/ Nrf2 | (349) |

AD, Alzheimer's disease; Aβ, amyloid β; APP/PS1, amyloid-β protein/presenilin-1; 5XFAD, 5X familial Alzheimer's disease; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; BACE1, β-site amyloid precursor protein cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; CREB, cyclic AMP response element binding; ERK, extracellular signal-regulated kinases; GFAP, glial fibrillary acidic protein; GSK-3β, glycogen synthase kinase-3β; HO-1, haem oxygenase-1; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IBA-1, ionized calcium binding adaptor molecule 1; interferon-γ, IFN-γ; JAK2, Janus kinase 2; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; NF-κB, nuclear factor-kappa-B; Nrf2, Nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; PGE2, prostaglandin E2; PPARs, Peroxisome proliferator-activated receptors; PTEN, phosphate and tensin homolog deleted on chromosome 10; PKA, protein kinase A; PKG, cGMP-dependent protein kinase; ROS, reactive oxygen species; STAT3, signal transducers and activators of transcription 3; SOCS, suppressor of cytokine signaling; TLRs, Toll-like receptors; WDFY1, WD repeat and FYVE domain-containing 1; p-phosphorylated; AP-1, activator protein 1.

IL-10, upregulated the expression of the cytokine signaling suppressor SOCS-1, blocked JAK2 and STAT3 phosphorylation and reduced the M1/M2 ratio of microglia phenotype in the same LPS-induced BV2 cell model, thereby ameliorating neuroinflammation from multiple perspectives (286).

NF-κB and STAT3 are two key regulators of cytokine production that can reciprocally modulate each other (288,289). Inhibition of STAT3 activation has been shown to reduce NF-κB activation, thereby attenuating amyloidogenesis and neuroinflammation (271,272). Ent-Sauchinone, a polyphenolic compound from the lignan family, exerts inhibitory effects on neuroinflammation and amyloidogenesis by blocking the STAT3/NF-κB pathway (271). In LPS-stimulated BV-2 microglia, ent-Sauchinone dose-dependently reduces the production of ROS and NO, as well as the expression of iNOS and COX-2, while inhibiting NF-κB activation and the elevated DNA-binding activity of STAT3 induced by LPS. Inhibition of neuroinflammation and prevention of neuroinflammation-induced Aβ production were further confirmed using short interfering RNA and pharmacological inhibitors of STAT3 (290). Sorafenib (291), an anti-cancer drug, also exerts anti-neuroinflammatory effects by modulating the AKT/P38-linked STAT3/NF-κB signaling pathway. It reduces the mRNA expression of pro-inflammatory cytokines in LPS-induced BV-2 microglia and inhibits the increase in STAT3 and NF-κB phosphorylation levels by inhibiting AKT and P38 signaling. An *in vivo* study further confirmed the anti-inflammatory effects of Sorafenib, suggesting its potential as a therapeutic agent to inhibit neuroinflammatory responses in the brain (291) (Fig. 4 and Table IV).

## 6. PI3K/Akt

The PI3K/Akt pathway is a vital signaling pathway that regulates a variety of transcription factors and cellular functions (292). Its association with various pathogenic factors of AD, including aging, Aβ and synaptic loss, has been uncovered (293). There are reports of reduced expression of the PI3K/Akt pathway in the brains of patients with AD, while upregulation of this pathway can alleviate tau-induced neurotoxicity and Aβ deposition (294), improve learning and memory capacity and reduce brain damage, and reduce inflammation and oxidative stress in mice with AD (295). Therefore, the role of the PI3K/Akt pathway in microglia has received increasing attention. Studies indicate that PI3K/Akt phosphorylation directly regulates NF-κB in microglia, suggesting a strong link between PI3K/Akt and neuroinflammation (296). GSK-3β signaling, which is involved in inflammation, oxidative stress, and apoptosis, can be activated by Akt phosphorylation upstream (297). Therefore, the Akt/GSK-3β signaling pathway, an important mediator of the inflammatory response, is closely linked to the PI3K/Akt pathway and the role of microglia.

DHCR24 (298), also known as 3-β-hydroxysteroid-Δ-24-reductase (seladin-1), exerts neuroprotective effects by participating in the degradation of amyloid precursor proteins, thereby preventing Aβ toxicity, endoplasmic reticulum stress and cellular oxidative damage, which are beneficial in both the prevention and treatment of AD (298-299). A recent study has revealed that DHCR24 can also exert anti-inflammatory effects by activating the Akt/GSK-3β signaling pathway (298). Lentivirus was used to overexpress DHCR24 in BV-2 cells and the results demonstrated that DHCR24 has the ability to attenuate the inflammatory response induced by $A\beta_{25-35}$ by altering the polarization phenotype of microglia (298). Further mechanistic analysis revealed that DHCR24 affected the protein expression levels of P-Akt and P-GSK-3β. Furthermore, the Akt inhibitor MK2206 attenuated this effect, thus demonstrating the neuroprotective function of DHCR24 in AD-associated inflammatory injury (298). Sulforaphene (SF) (300) is an isothiocyanate derived from Raphani Semen (301). SF inhibits neuroinflammation by modulating the PI3K/Akt/GSK-3β pathway (300). In rats treated with intravenous streptozotocin (STZ), SF treatment significantly improved STZ-induced cognitive impairment, inhibited the production of pro-inflammatory factors and promoted the release of anti-inflammatory factors. Additionally, SF increased the ratio of p-Akt/Akt and p-GSK-3β/GSK-3β in the rat hippocampus (300). In LPS-stimulated BV-2 cells, SF exerted significant inhibitory effects on the release of NO, TNF-α, and IL-6, while also affecting the nuclear translocation of p-NF-κB p65 and the p-GSK-3β (Ser9)/GSK-3β ratio (300). Therefore, SF shows promising potential as a neuroprotective agent and could be further developed as a therapeutic treatment for AD (Fig. 4 and Table IV).

## 7. CREB

The cyclic AMP response element binding (CREB) is a stimulus-inducible transcription factor that dimers with the conserved cyclic AMP response element (CRE) (302) to activate CRE-responsive genes in response to extracellular stimuli (303). In the CNS, CREB regulates various protein kinases, including protein kinase A (PKA) and MAPKs, which are involved in neuronal development, synaptic plasticity, short-term to long-term memory conversion and neuroprotection in the CNS (304,305). Furthermore, dysregulated CREB phosphorylation has been identified in AD mouse models (306) and patients with AD (307), demonstrating the important role of CREB in the pathogenesis of AD (308). Notably, CREB has been found to be associated with neuroinflammation and may be an effective therapeutic target for the treatment of AD (309). Phosphorylation of CREB has been shown to reduce neuroinflammation by regulating NF-κB to block the transcription of inflammatory mediators (310). Moreover, phosphorylation of CREB promotes the production of anti-inflammatory cytokines in activated microglia that induce microglia inactivation or polarization to the M2 phenotype (311), thus modulating neuroinflammation for neuroprotection in AD.

The cGMP-dependent protein kinase (PKG) plays an important role in mediating the transcriptional regulation of CREB by phosphorylating CREB and activating different downstream genes (312). In an aged Tg APP/PS1 mouse model, sildenafil was found to be effective in reducing neuroinflammation and Aβ levels in the brain. Specifically, sildenafil suppressed Aβ-induced pro-inflammatory factors in the hippocampus, and this effect was mediated through the PKG/CREB signaling pathway (313). Inhibition of PKG in the hippocampus prior to sildenafil injection resulted in blocked CREB phosphorylation, resulting in a reduced production of inflammatory factors and ultimately produced anti-inflammatory effects. Furthermore,

there is ample evidence in the literature to support the crucial role of the PKA/CREB pathway as a drug target in AD (314), particularly in the context of downregulation of the transcriptional cascade that contributes to the disease. Additionally, inhibition of histamine H3 receptors (H3R) has been shown to improve cognitive deficits in AD (315,316). The histamine H3R antagonist, thioperamide (317), can effectively inhibit inflammatory cell recruitment (318), further highlighting the importance of the PKA/CREB pathway in modulating neuroinflammation as a therapeutic target for AD. It has been found that thioperamide exerts its effects on the PKA/CREB signaling pathway, suppressing microglia activity and promoting their conversion from M1 to M2 phenotype, ultimately impeding LPS-induced neuroinflammation and restoring cognitive function in mice (317). Mechanistically, the downstream PKA/CREB pathway activated by H2R stimulation triggers CBP (CREB-CREB binding protein) interactions that facilitated the release of anti-inflammatory factors and brain-derived neurotrophic factor, while simultaneously attenuating NF-κB-CBP interactions to reduce the secretion of pro-inflammatory factors. These effects were found to be reversible by cimetidine (H2R antagonist) but not by piramine (H1R antagonist), indicating a novel H2R-dependent histamine-mediated mechanism underlying the therapeutic effects of thioperamide on neuroinflammation (317) (Table IV).

## 8. Nrf2

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that plays a crucial role in regulating oxidative stress in various cell types, including glial cells and neurons (319). Notably, a reduction in Nrf2 expression has been detected in the brains of patients with AD (320). Moreover, a growing body of research indicates that augmenting Nrf2 signaling has the potential to improve Aβ-induced neurodegeneration and oxidative stress in *in vitro* and *in vivo* models of AD (321). Such investigations have also revealed that enhancing Nrf2 signaling can alleviate microglia-mediated inflammation in the brain (322), highlighting the potential for therapeutic intervention targeting Nrf2 in the development of drugs for the treatment of AD.

Studies have shown that certain herbs and natural products contain active ingredients that can interfere with Nrf2, thereby inhibiting neuroinflammation. For example, Methysticin (323), a kavalactones derived from the Piperaceae plant kava (324), has been demonstrated to inhibit neuroinflammation and oxidative damage and to attenuate long-term memory loss in APP/PS1 mice. These effects are attributed to its ability to significantly reduce microglia activation and the secretion of pro-inflammatory factors in the hippocampus and cortex, possibly mediated by Nrf2. Similarly, a polyphenol extract derived from *Arabidopsis thaliana* was found to have anti-inflammatory activity in transgenic AD flies and $A\beta_{25-35}$-induced BV2 cells by influencing the nuclear translocation of Nrf2 and NF-κB (325). Gracilin A, a natural product isolated from the marine sponge *Spongionella gracilis* (326), has been associated with Nrf2-involved inflammation. An *in vitro* study has shown that Gracilin A reduces the release of pro-inflammatory factors from BV2 cells induced by LPS by inhibiting the expression of iNOS and the activation of p38 MAPK, which affects the translocation of NF-κB p65 and Nrf2 (327).

Kelch-like ECH-associated protein 1 (Keap1), as an adapter protein, inhibits the function of Nrf2 by degrading it in the normal state of the cell (328). However, when cells are exposed to external stimuli, the degradation of Keap1 (dependent on Nrf2), is inhibited, leading to the accumulation of Nrf2 in the nucleus and its regulatory role in the expression of various antioxidant genes (329). Engeletin, a flavonol glycoside derived from the leaves of Engelhardia roxburghiana (330), has demonstrated anti-inflammatory properties. Specifically, it has been shown to inhibit the expression and secretion of $A\beta_{1-42}$-induced pro-inflammatory factors and to enhance the activation of the Keap1/Nrf2 pathway in BV-2 cells. However, when Nrf2 was knocked down, the inhibitory effect of Engeletin was reversed. These findings further underscore the potential of pharmacological intervention targeting the Keap1/Nrf2 pathway in anti-AD therapy (331).

Haem oxygenase-1 (HO-1), a stress-inducible protein, exerts a protective effect against inflammatory and oxidative stress and has been shown to be beneficial in neurodegenerative diseases including AD (332). The promotion of HO-1 expression is mediated by Nrf2 (333). Study has shown that Bambusae Caulis in Taeniam ethyl acetate fraction (BCE) (334) as a modulator of Nrf2 signaling, regulates the neuroprotective and anti-neuroinflammatory effects of microglia BV2 by modulating the expression of HO-1. BCE was shown to inhibit the production of pro-inflammatory mediators and cytokines in LPS-induced BV2 cells, while upregulating the mRNA and protein expression levels of HO-1, and influencing the accumulation and transactivation of Nrf2 in the cells (334). Further evidence for the involvement of HO-1 in the observed anti-inflammatory effects of BCE was obtained by using the selective HO-1 inhibitor, SnPP, which reversed these effects (334).

Researchers have identified multiple inhibitors that act on multiple pathways to inhibit neuroinflammation by targeting Nrf2. Among these inhibitors, L-F001 (335), a newly developed ROCK inhibitor, has shown promise in the treatment of AD by inhibiting NF-κB and activating Nrf2. An *in vitro* study has demonstrated that L-F001 significantly inhibits the expression of iNOS and COX-2 as well as the secretion of pro-inflammatory mediators in BV-2 cells following LPS induction (335). This is accompanied by inhibition of NF-κB signaling and upregulation the expression of HO-1 and glutamate cysteine ligase modifier subunit, downstream effectors of Nrf2 (335). Similarly *in vivo* experiments, on mice have confirmed that L-F001 significantly reduces the levels of pro-inflammatory mediators induced by LPS, in line with the *in vitro* findings (335). In addition, the researchers have found that G protein-coupled receptor 17 was expressed in neurons and microglia (336) and that its antagonist, cangrelor (337), had an inhibitory effect on neuroinflammation. In a mouse model of AD with intracerebroventricular injection of $A\beta_{1-42}$, cangrelor reduced BACE1 activity as well as $A\beta_{1-42}$ levels in the hippocampus and frontal cortex of mice, while inhibiting microglia activation and levels of pro-inflammatory factors through a mechanism involving Nrf2/HO-1 and NF-κB signaling (337). Another inhibitor, β-naphthoflavone (BNF) (338), a derivative of a natural flavonoid widely used in

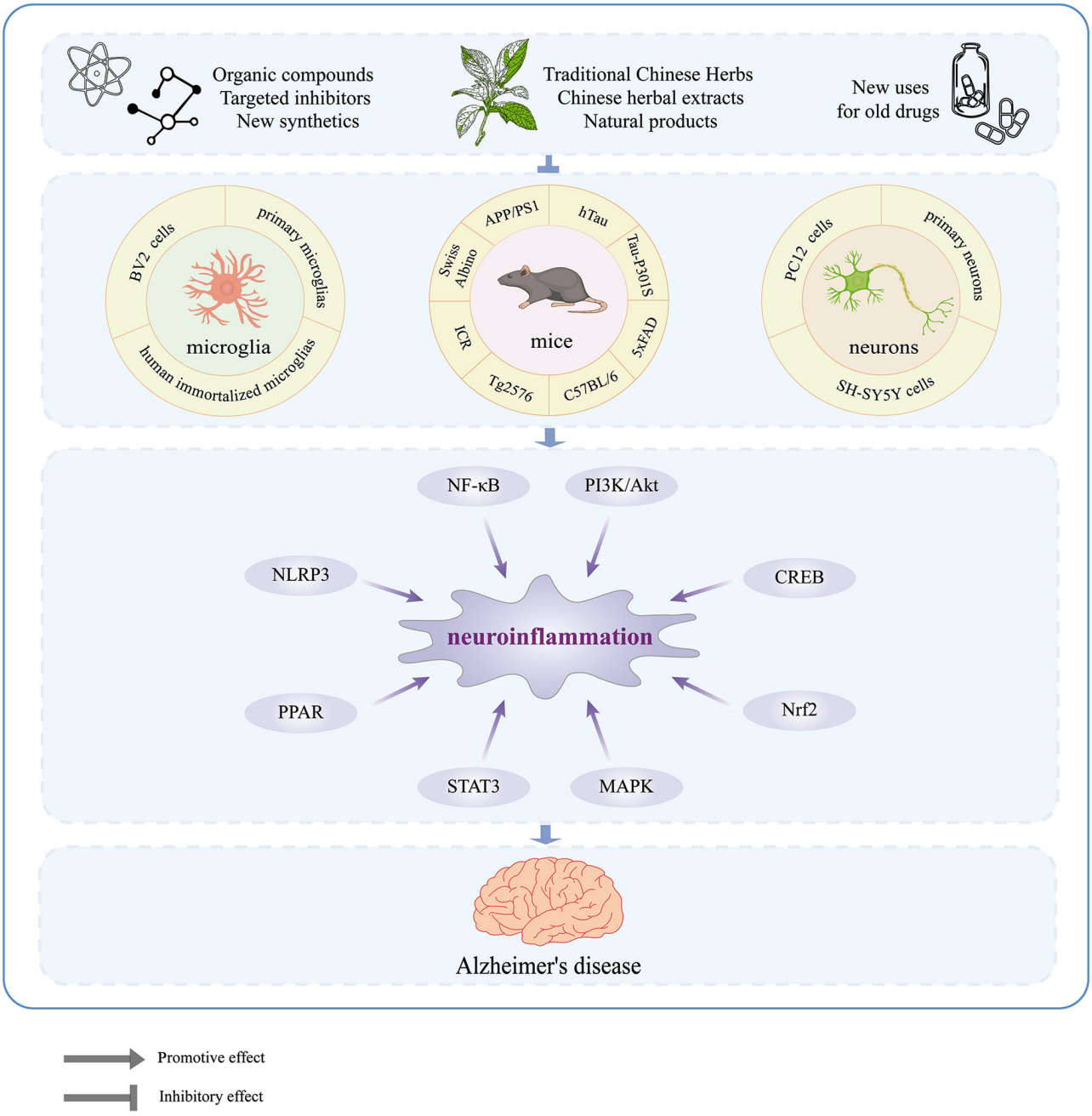


Figure 5. Targeting inflammatory signaling pathways with drugs shows promise in AD treatment. By modulating various signaling pathways, drugs and inhibitors can effectively target microglia, neurons, and mice with AD. This targeted approach helps regulate inflammatory responses, promote neuronal survival, and restore functional recovery, ultimately alleviating symptoms of AD. AD, Alzheimer's disease; NLRP3, NOD-like receptor thermal protein domain associated protein 3; CREB, cyclic AMP response element binding; PPAR, Peroxisome proliferator-activated receptor; Nrf2, Nuclear factor erythroid 2-related factor 2.

the pharmaceutical industry, has antioxidant and anti-inflammatory effects. Pretreatment with BNF was found to inhibit activation of the NF-κB pathway in LPS-treated BV-2 cells, promote AKT activation, enhance the nuclear translocation of Nrf2, lead to an upregulation of the HO-1 protein levels, and significantly reduce the expression of pro-inflammatory mediators (338). The use of MK2206 (an AKT inhibitor), RA (an Nrf2 inhibitor) and SnPP IX (an HO-1 inhibitor) further confirms that BNF inhibits the production of pro-inflammatory mediators by activating this pathway (338).

AMPK is an important cellular metabolic sensor and regulator (339) that is expressed in peripheral tissues and particularly in neuronal cells in the brain (340). Reports show that AMPK is hyperactivated in neurons from patients with AD (341) and impaired in the hippocampus of APP/PS1 mice (342), and is involved in Aβ clearance (343) and tau phosphorylation (344). AMPK has also been associated with neuroinflammation (345) and is dependent on microglia regulation (346). A link between AMPK and the Nrf2/ARE pathway has been suggested (347,348) and Bakkenolide B (349), the major constituent of *Petasites japonicus* leaves (350), has been found to activate the AMPK/Nrf2 signaling pathway. An *in vitro* study demonstrated that Bakkenolide B significantly reduces LPS-mediated production of pro-inflammatory factors

in microglia and upregulates the expression of Nrf2-associated downstream effectors, such as NQO-1 and HO-1 (349). Knockdown of Nrf2, HO-1, and NQO-1 attenuated the anti-inflammatory effects of Bakkenolide B, whereas AMPK inhibitors reversed these effects. These findings indicate that Bakkenolide B induces the AMPK/Nrf2 signaling pathway to reduce neuroinflammation (349) (Table IV).

## 9. Conclusion and future perspectives

The pathogenesis of AD is a multifaceted process, but studies ranging from cellular and animal models, as well as studies involving patients with AD, have unequivocally established the pivotal role of neuroinflammation. Excessive activation of microglia releases inflammatory mediators that contribute to the pathological features of AD. Thus, inhibiting microglia-mediated inflammation is a promising approach to combat this disease.

Intracellular signaling pathways play a crucial role in maintaining cellular function and metabolism and are intricately associated with the pathogenesis of AD, including neuroinflammation. It is worth noting that these signaling pathways are complex, interconnected and capable of interacting with each other. By intervening in the pertinent signaling pathways through the use of drugs or inhibitors, it is possible to inhibit neuroinflammation and exert an effect on AD. Therefore, this review focused on neuroinflammation in AD and presented a comprehensive synthesis and summary of the mechanisms of action and potential signaling proteins linked with inhibitors, herbal medicines, and their active ingredients and metabolites, from the standpoint of signaling pathways (Fig. 5).

Various drugs or inhibitors can regulate various signaling pathways, and multiple drugs can also target the same pathway. It is worth noting that NF-κB, MAPK, and NLRP3 are key signaling molecules targeted in neuroinflammation and have been extensively studied in drug discovery. By interfering with one or more of these signaling pathways, drugs can synergistically modulate multiple targets, achieve a balance between antioxidant and pro-inflammatory effects, and ultimately improve cognitive impairment in patients with AD (refer to Fig. 1 for details). Given the complexity of AD pathogenesis, drugs or inhibitors with multi-level and multi-target potential hold promise as a breakthrough in AD drug development. Exploring the anti-inflammatory effects of commonly used clinical drugs may broaden their potential application. However, current research is still primarily focused on animal and cellular experiments, with a focus on LPS- or Aβ-stimulated BV2 microglia. Although a number of problems have prevented a number of drugs from entering clinical trials, inhibitors, that target neuroinflammation remain a potentially promising therapeutic option for AD.

In summary, the present review highlighted the prominent role of neuroinflammation in AD pathology and reviewed various anti-inflammatory inhibitors targeting molecular targets and signaling pathways. These inhibitors have shown significant potential as drug treatments for AD and have provided a foundation for the further development of novel AD therapeutics. However, the specificity, efficacy, safety, and availability of these inhibitors, natural ingredients and metabolites, are critical considerations for their clinical application. Moreover, further studies on their pharmacokinetic profiles and underlying mechanisms are necessary for the development of novel AD therapeutics. Despite these challenges, the potential benefits of these drugs underscore the need for continued research into their efficacy as treatments for AD.

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## Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

## Authors' contributions

YZ wrote the original draft of the manuscript. ZW, RZ and XZ reviewed and edited the manuscript. QG, JG and PX produced the diagrams and charts. XJ and LY contributed to the conception, design and drafting of the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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