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NLRP3 inflammasome in Alzheimer's disease: molecular mechanisms and emerging therapies

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuroinflammation, with no definitive cure currently available. The NLRP3 inflammasome, a key mediator of neuroinflammation, has emerged as a critical player in AD pathogenesis, contributing to the accumulation of β-amyloid (Aβ) plaques, tau hyperphosphorylation, and neuronal damage. This review explores the mechanisms by which the NLRP3 inflammasome is activated in AD, including its interactions with Aβ, tau, reactive oxygen species (ROS), and pyroptosis. Additionally, it highlights the role of the ubiquitin system, ion channels, autophagy, and gut microbiota in regulating NLRP3 activation. Therapeutic strategies targeting the NLRP3 inflammasome, such as IL-1β inhibitors, natural compounds, and novel small molecules, are discussed as promising approaches to mitigate neuroinflammation and slow AD progression. This review underscores the potential of NLRP3 inflammasome inhibition as a therapeutic avenue for AD.

KEYWORDS

NLRP3, neuro-inflammation, IL-1β, inflammasome, Alzheimer's disease, microglia, inhibitor

1 Introduction

Alzheimer's disease (AD) is a prevalent, chronic, and progressive neurodegenerative disorder, often leading to significant cognitive decline and memory impairment in its early stages, with later phases causing substantial daily functioning challenges and psychiatric symptoms (1). Currently, there are no definitive strategies for the prevention or treatment of AD (2), and its incidence is escalating rapidly due to global aging trends (3). The pathogenesis of AD is primarily associated with the accumulation of β-amyloid (Aβ), hyperphosphorylation of tau proteins, and the formation of neurofibrillary tangles. Recent studies have further underscored the critical role of neuroinflammation in the progression of AD (4, 5).

Among the various neuroinflammatory mediators, the NLRP3 inflammasome has gained attention as a potential therapeutic target (6). First described by Martinon et al. (7), the inflammasome is a multi-protein complex that includes caspases, ASC, and cytoplasmic pattern recognition receptors (8). It recognizes pathogen- or danger-associated molecular patterns, activating Caspase-1, which processes IL-1β and IL-18 precursors into active cytokines (9–11). NLRP3, the most extensively studied inflammasome, has been implicated in the pathogenesis of AD (10, 12) This review summarizes the structure, activation mechanisms, and involvement of the NLRP3 inflammasome in AD, as well as potential therapeutic strategies targeting this inflammasome.

2 The role of NLRP3 inflammasome in Alzheimer's disease

2.1 Aβ, microglia, and NLRP3 activation

In brain regions affected by AD, microglia are frequently observed in proximity to Aβ plaques. Research has demonstrated that these microglial cells play a crucial role in eliminating Aβ through mechanisms such as phagocytosis and proteolysis (13). The activation of the NLRP3 inflammasome, however, is not solely triggered by fibrillar Aβ but also by smaller Aβ oligomers and protofibrils (14). Aβ induces microglial activation through multiple signaling pathways, including NF-κB, which upregulates the expression of NLRP3 and pro-IL-1β (15). Moreover, soluble Aβ disrupts lysosomal stability, leading to the release of cathepsins and subsequent activation of the NLRP3 inflammasome (16). Additionally, Aβ oligomers impair mitochondrial function, causing oxidative stress and the release of mitochondrial DNA, which further exacerbates NLRP3 inflammasome activation (17). As AD progresses, chronic NLRP3 activation leads to excessive microglial activation, diminishing their ability to clear Aβ and fostering its accumulation (18, 19). Notably, APP/PS1 transgenic mice lacking NLRP3 exhibit reduced Aβ deposition, suggesting that NLRP3 contributes to Aβ accumulation and accelerates disease progression (20).

2.2 Tau-induced NLRP3 inflammasome activation

Tau proteins activate the NLRP3 inflammasome in microglial cells via an ASC-dependent mechanism, triggering IL-1β release and neuroinflammation (16, 21). This activation also regulates tau phosphorylation by modulating kinases and phosphatases, leading to tau hyperphosphorylation and aggregation in neurons (22). Hyperphosphorylated tau aggregates (NFTs) are recognized by microglial TLRs, inducing NLRP3 inflammasome assembly through the NF-κB pathway. Additionally, tau uptake by microglial lysosomes can release cathepsin B, further activating the inflammasome. The resulting IL-1β and IL-18 release exacerbates neuroinflammation and accelerates AD (23). Tau precursors can also trigger neuroinflammation and impair memory through NLRP3 pathways (22). Thus, targeting NLRP3 activation may offer a potential AD therapy.

2.3 ROS and NLRP3 inflammasome

ROS are crucial regulators of the NLRP3 inflammasome, with their generation closely linked to enzymes such as peroxiredoxin and NADPH oxidase (24). In normal conditions, thioredoxin (TRX) and its binding partner thioredoxin-interacting protein (TXNIP) form a stable complex. However, under oxidative stress, an increase in ROS levels leads to the oxidation of TRX, which in turn neutralizes ROS and causes the dissociation of the TRX-TXNIP complex (25). This dissociation allows TXNIP to interact with NLRP3, thereby recruiting ASC and procaspase-1, which ultimately promotes the assembly and activation of the inflammasome (26). Furthermore, mitochondrial dysfunction can lead to the release of mitochondrial DNA, a potent activator of the NLRP3 inflammasome (27). Different ROS sources selectively modulate NLRP3 signaling in AD (28). Mitochondrial ROS from electron transport chain (ETC) dysfunction exacerbates oxidative damage, impairing neuronal energy metabolism and enhancing NLRP3 activation (29). Conversely, NADPH oxidase-derived ROS, particularly NOX2 in microglia, amplifies ROS production, potentiating NLRP3 signaling and neuroinflammation (30). Targeting these distinct ROS pathways is crucial for precise NLRP3 inhibition in AD.

2.4 Pyroptosis mediated by NLRP3 inflammasome

Pyroptosis, an inflammatory programmed cell death, is activated by the NLRP3 inflammasome in AD (31). It promotes pro-inflammatory cytokine secretion, aiding Aβ plaque clearance but also inducing chronic neuroinflammation that accelerates AD progression (32). This process is mediated by gasdermin D (GSDMD) cleavage and caspase-1 activation (33). Pyroptosis occurs via two pathways: (1) The Classical Pathway, where caspase-1 cleaves IL-1β and IL-18 precursors, producing mature cytokines, and modifies GSDMD to form membrane pores, releasing cytokines and driving pyroptosis; and (2) The Non-classical Pathway, where caspase-11 (mice) or caspase-4/5 (humans) is activated by cytosolic LPS, triggering pyroptosis through specific cleavage (34, 35). In AD, Aβ-induced pyroptosis is mediated by the NLRP3-caspase-1-GSDMD axis, exacerbating neuroinflammation and neuronal damage (36–38). GSDMD knockout inhibits astrocyte pyroptosis, mitigating Aβ42-induced brain and vascular damage in APP/PS1 mice (39). These findings suggest that targeting inflammasome-driven pyroptosis holds potential as a novel therapeutic approach for AD.

2.5 Integration of Aβ, Tau, ROS, and Autophagy Pathways

Recent studies highlight the interconnected mechanisms of Aβ accumulation, tau hyperphosphorylation, ROS generation, and defective autophagy in driving AD progression (34). Aβ and tau aggregates activate microglia, increasing ROS and NLRP3 inflammasome activation, which exacerbates mitochondrial dysfunction and impairs autophagy (40). This creates a vicious cycle in which NLRP3 serves as a pivotal intersection point, amplifying neuroinflammation and neuronal damage (40). Targeting NLRP3 offers a promising therapeutic strategy to disrupt these cascades, addressing the complex interplay of Aβ, tau, ROS, and autophagy in AD (Figure 1).

3 Mechanisms of NLRP3 inflammasome promoting AD progress

3.1 Ubiquitin system

Ubiquitin, a small protein present in all eukaryotic cells, is capable of forming chains through enzymatic processes, which signal target proteins for degradation (41). This modification, referred to as ubiquitination, is carried out by a series of specialized enzymes that alter target proteins, marking them for proteasomal recognition and breakdown (42). In conjunction with autophagy, this system plays a critical role in maintaining cellular homeostasis (43). Disruptions in the ubiquitin-proteasome pathway have been linked to Alzheimer's disease and other neurodegenerative conditions (44). Within the E1, E2, and E3 enzyme families, E3 ligases such as SCF-FBXL2 selectively target NLRP3 and its associated molecules, including ASC and caspase-1, promoting NLRP3 ubiquitination and proteasomal degradation, thereby regulating its activation (45). Additionally, Cullin1 associates with NLRP3, enhancing its ubiquitination but without triggering degradation, which serves to inhibit NLRP3 inflammasome activation (46).

3.2 Ion channels

Ion channels play a critical role in modulating the activation of the NLRP3 inflammasome, with K^+ efflux identified as a pivotal signaling event (47). In AD, imbalances in the homeostasis of Na^+ and K^+ disrupt the electrophysiological properties of neurons, contributing to the pathophysiological change characteristic of the disease (48). Studies by Gritsenko A et al. (49) demonstrated that K^+ efflux in human monocytes leads to the aggregation of ASC,

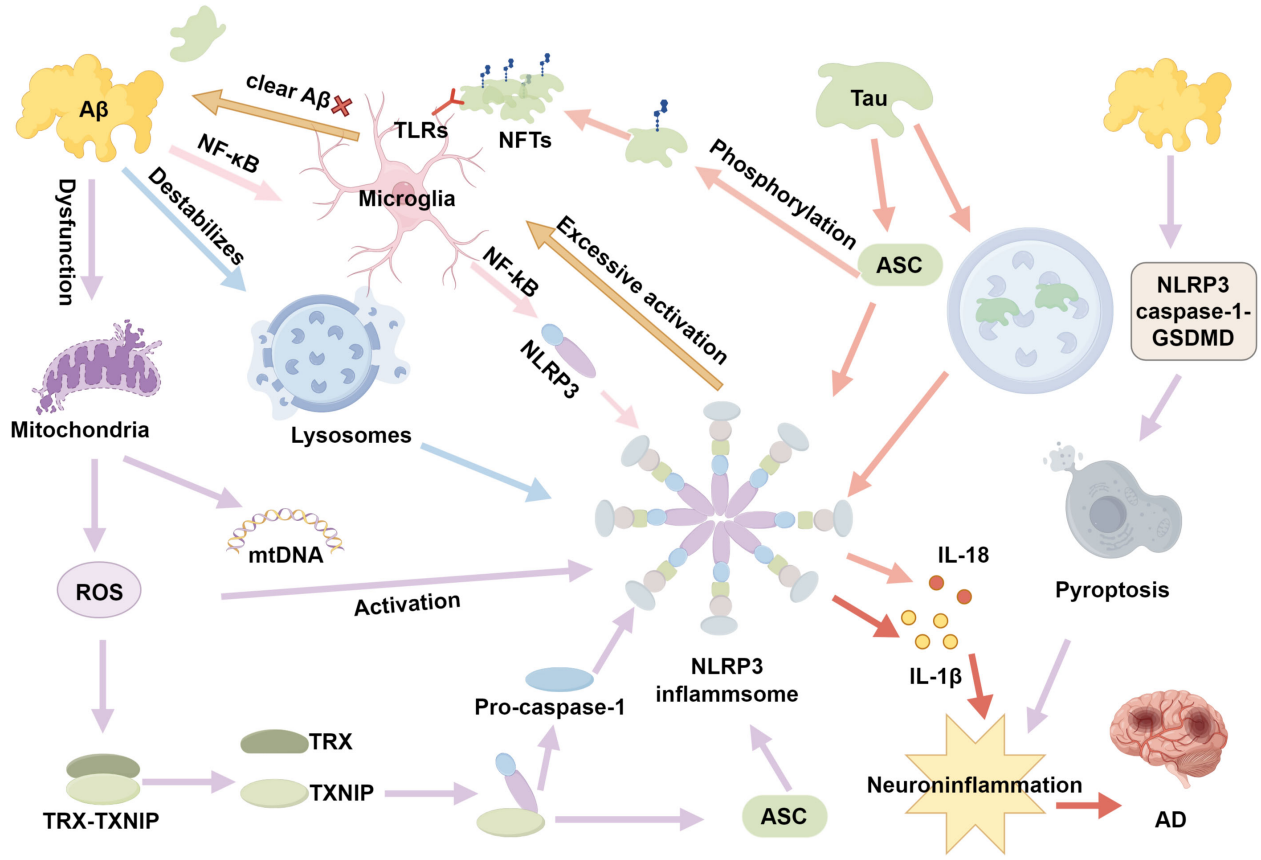

FIGURE 1
The role of NLRP3 inflammasome in AD.

cleavage of caspase-1, and subsequent processing of GSDMD. Inflammatory factors significantly influence the efficacy of therapies for inflammatory diseases (50–55). Inhibition of NLRP3 or genetic deletion of NLRP3 and GSDMD blocks the release of IL-18, highlighting the crucial role of early inflammasome assembly before IL-1β production (56). Additionally, extracellular ATP, released in response to bacterial toxins, activates P2X7 purinergic receptors, which disturb intracellular ion balance and promote K^+ efflux (57). This perturbation enables the assembly of NLRP3 with ASC, forming an active inflammasome complex that cleaves procaspase-1 into active caspase-1. Caspase-1 then facilitates the secretion of IL-1β and IL-18 (58). Furthermore, GSDMD is cleaved by the inflammasome, creating membrane pores that allow the release of these cytokines (45).

3.3 Autophagosomes and lysosomes

Autophagy is a fundamental cellular process in eukaryotic cells that degrades and recycles cytoplasmic components, such as damaged organelles and protein aggregates, to maintain cellular homeostasis (59). Wang D et al. (60) revealed that excessive accumulation of manganese compromises lysosomal integrity by altering their structure and impairing their function. In manganese-induced NLRP3-caspase-1 inflammasome activation, the release of cathepsin B from lysosomes plays a critical role (61). Additionally, inflammatory stimuli such as alum, crystalline materials, and protein aggregates can trigger autophagy (62), leading to lysosomal destabilization and rupture (63). Following lysosomal rupture, cathepsin B is released and directly interacts with NLRP3, thereby promoting the activation of the NLRP3 inflammasome (62).

3.4 ROS production

In AD pathogenesis, Aβ peptides compromise synaptic plasticity and inhibit long-term potentiation (64). Parajuli et al. showed that Aβ promotes the conversion of pro-IL-1β into its active form, IL-1β, thereby enhancing microglia-mediated neurotoxicity (65). This process is largely driven by increased caspase-1 activity and the activation of NOD-like receptors, specifically NLRP3, which features a pyrin domain (66). Mitochondrial-derived ROS, and to a lesser degree, ROS generated by NADPH oxidase, play a pivotal role in initiating NLRP3 activation (67). Elevated ROS levels activate TRPM2 channels, which subsequently activate NLRP3 and caspase-1, thereby increasing IL-1β production (68). Notably, the use of mitochondrial ROS inhibitors, such as DPI, significantly reduces both ROS and IL-1β levels, indicating a suppression of NLRP3 activation (69).

3.5 Gut microbiota

GM, a consortium of symbiotic microorganisms within the human intestinal tract, has been implicated in various diseases, including AD. Dysbiosis, or disruptions in microbial composition, is frequently observed in individuals with AD (70). The gut-brain axis, an increasingly studied area, highlights how microbiota influences brain function, with both probiotics and prebiotics playing roles in modulating microbial and immune systems (71). Dysbiosis impairs the intestinal barrier, allowing pathogen-associated molecular patterns (PAMPs) to trigger the release of pro-inflammatory cytokines. These cytokines can then travel to the brain, aggravating the progression of AD (72–74). Moreover, microbial activation of the NLRP3 inflammasome leads to the upregulation of caspase-1 in the AD brain, further advancing disease pathology (75). While short-chain fatty acids (SCFAs) from commensal bacteria bind GPCRs (GPR43, GPR41), inhibit HDACs, reduce cytokines, and downregulate NLRP3 in microglia/astrocytes (76). Thus, restoring a balanced gut microbiota may reduce neuroinflammation and enhance cognitive function in AD patients (77).

4 Therapeutic strategies targeting the NLRP3 inflammasome

4.1 IL-1β modulation in NLRP3-targeted Alzheimer's therapy

Early therapeutic strategies targeting the NLRP3 inflammasome pathway have largely focused on IL-1β modulation. Notable agents with proven efficacy include anakinra, a recombinant IL-1 receptor antagonist; canakinumab, a monoclonal antibody against IL-1β; and rilonacept, a soluble decoy receptor that binds IL-1β by incorporating IL-1R1 and IL-1RAcP domains (78). In preclinical experiments using the 3xTg AD model, anakinra was shown to reduce Aβ and tau accumulation, decrease IL-1β levels, and enhance cognitive function (79). Furthermore, both anakinra treatment and genetic deletion of IL-1R improved mitochondrial dysfunction and alleviated memory deficits associated with Aβ in *in vivo* and *in vitro* models (80). Despite these promising results, the challenge of the blood-brain barrier (BBB) has hindered further exploration of IL-1β-based therapies in AD (80). A Phase 2 clinical trial assessing the efficacy of canakinumab in AD patients is currently ongoing (NCT04795466). However, since IL-1β acts as a downstream effector, directly targeting NLRP3 or its inflammasome components could potentially offer more substantial therapeutic advantages (81).

4.2 Ginkgolide B and sulforaphane

GB has demonstrated protective effects against ischemic brain injury and neurotoxicity induced by Aβ (82). In models of hypoxic-ischemic brain damage in rats, GB diminishes NLRP3 inflammasome activation, thereby alleviating neuroinflammation and mitigating AD-related pathology in BV2 cells (83). Additionally, GB treatment has been reported to reduce Aβ-induced pathological alterations and inhibit NLRP3 inflammasome activation (84). Furthermore, GB

promotes the upregulation of anti-inflammatory markers in M2 microglia, while concurrently suppressing the release of pro-inflammatory cytokines in M1 microglia (85). Through autophagy-dependent pathways, GB also curbs NLRP3 inflammasome activation, ultimately safeguarding cognitive function in SAMP8 mice (84, 86).

SFN exhibits notable anti-inflammatory, antioxidant, and neuroprotective properties (87). Studies suggest that SFN effectively diminishes the release of IL-1β and IL-18 in LPS-activated microglia, while also inhibiting the overexpression of NLRP3 and caspase-1 proteins (88). Furthermore, SFN prevents pyroptosis in microglia by inhibiting caspase-1 activity (89), and attenuates NLRP3 inflammasome activation via the downregulation of NF-κB (88), thus reducing inflammatory responses (90).

4.3 Dapansutrile (OLT1177) and MCC950

OLT1177, an orally available and selective inhibitor of the NLRP3 inflammasome, has demonstrated considerable therapeutic promise (91). This compound binds directly to NLRP3, blocking its ATPase function and disrupting several inflammasome activation pathways. In APP/PS1 transgenic mice, OLT1177 treatment partially alleviated cognitive impairments as assessed by the Morris water maze test. It also decreased microglial activation and lowered cortical plaque accumulation (92). Although there is limited research on its application in neurodegenerative disorders, OLT1177's excellent safety profile, favorable pharmacokinetic characteristics, and minimal side effects underscore its potential as a therapeutic agent for AD (93).

MCC950 is a potent anti-inflammatory compound that selectively inhibits NLRP3 inflammasome activation by targeting its NACHT domain (94). In models of Alzheimer's disease, MCC950 effectively dampens the inflammasome activation triggered by Aβ or tau, preventing the cleavage and release of caspase-1 and IL-1β. Additionally, it completely halts immune responses induced by Aβ aggregates and low-molecular-weight oligomers (95). *In vitro* experiments using Aβ-stimulated human primary neurons pre-treated with MCC950 demonstrated its capacity to inhibit pyroptosis, thereby significantly reducing Aβ-induced neuronal toxicity. Other NLRP3 inhibitors currently under exploration include IFM-514 (96), CY-09 (97), DFV890 (98), Tranilast (99), Oridonin (100), Selnolast (101), and Inzomelid (102).

4.4 Other therapeutic strategies targeting the NLRP3 inflammasome

Nonsteroidal anti-inflammatory drugs (NSAIDs) have shown potential in delaying the onset of Alzheimer's disease (AD) or reducing its risk, likely through their modulation of the NLRP3 inflammasome pathway (103). For instance, indomethacin, a well-known NSAID, has been demonstrated to inhibit both NLRC4 and NLRP3 inflammasomes. This inhibition leads to a reduction in the expression of IL-1β and caspase-1, thereby alleviating neuroinflammation and mitigating memory deficits associated with AD (104). MicroRNAs have been shown to suppress NLRP3 expression, leading to improved cognitive function in rodent models

TABLE 1 The therapies targeting NLRP3 Inflammasome in AD.

Therapeutic Strategy	Mechanism	Effect
Targeting IL-1β (Anakinra)	Modulates IL-1β activity by using IL-1 receptor antagonists, monoclonal antibodies, and decoy receptors.	Reduce IL-1β, improve cognitive function, and alleviate neuroinflammation.
Ginkgolide B (GB)	Inhibits NLRP3 inflammasome activation and reduces neuroinflammation.	GB reduces Aβ-induced pathology, enhances M2 microglia, suppresses pro-inflammatory cytokines, and improves cognitive function.
Sulforaphane (SFN)	Inhibits NLRP3 inflammasome activation via NF-κB downregulation and reduces pyroptosis.	SFN diminishes IL-1β/IL-18 release, inhibits caspase-1, and reduces NLRP3 overexpression in LPS-activated microglia. Shows anti-inflammatory and neuroprotective effects.
Dapansutrile (OLT1177)	Selectively inhibits NLRP3 inflammasome by blocking ATPase function and inflammasome activation.	OLT1177 improves cognitive function, reduces microglial activation, and lowers Aβ plaque accumulation in AD mouse models. Favorable pharmacokinetic properties.
MCC950	Selectively inhibits NLRP3 inflammasome via NACHT domain targeting.	MCC950 inhibits inflammasome activation by Aβ/tau, reducing IL-1β release and preventing neuronal toxicity in AD models.
Ketone Bodies	Ketogenic diets and ketone bodies (e.g., β-hydroxybutyrate) inhibit NLRP3 inflammasome activation and reduce Aβ buildup.	β-Hydroxybutyrate inhibits NLRP3 inflammasome, reduces Aβ internalization, and mitigates AD progression. 2-DG enhances bioenergetic capacity and promotes Aβ clearance.
Other Strategies	NSAIDs, microRNAs, autophagy, mitophagy, and botanical extracts modulate NLRP3 inflammasome activity.	Indomethacin, miR-138–5p, miR-223, Quercetin, Ginkgo biloba, and others reduce NLRP3 activation, improving cognition and reducing neuroinflammation.
New Therapies	Targets autophagy, mitophagy, and inflammasome activation.	Cornuside, Thonningianin A, and Eriodictyol inhibit NLRP3 inflammasome activation, promote mitophagic flux, and improve cognitive function in AD models.

of Alzheimer's disease (105, 106). In AD patients, reduced miR-22 levels in AD patients are associated with increased NLRP3 activation, while overexpression of miR-22 inhibits GSDMD-mediated pyroptosis, thereby reducing neuroinflammation and cognitive decline in AD mice (107). These findings highlight the potential of targeting miRNAs to modulate NLRP3 activity as a novel therapeutic strategy for AD.

In addition to miRNAs, autophagy and mitophagy also modulate NLRP3 activation. For example, IIIM-941 has been shown to induce autophagy via AMPK, inhibiting NLRP3 activity (108). A-68930 activates dopamine D1 receptors, promoting NLRP3 degradation through AMPK/autophagy, reducing IL-1β/IL-18 secretion, and mitigating Aβ1-42-induced neuroinflammation (109). Ginkgo biloba extract EGb 761 enhances microglial autophagy, downregulates NLRP3, and attenuates Aβ-induced IL-1β/caspase-1 activation in TgCRND8 mice (110). Furthermore, Quercetin stimulates mitophagy, suppressing mtROS-driven NLRP3 activation and protecting against neuronal damage (111). These studies suggest that enhancing autophagy and mitophagy in microglia may offer a promising therapeutic approach for AD.

4.8 New therapies focus on the NLRP3 inflammasome

A recent study has identified cornuside as a promising anti-AD agent. Cornuside has been shown to restores mitophagic flux, enabling the efficient the removal of damaged mitochondria and the recovery of mitochondrial function. These mechanisms contribute to the inhibition of NLRP3 inflammasome activation, thereby reducing neuronal and synaptic damage and improving cognitive function (112). Structurally unique diterpenoids, isolated from the mangrove plant *Excoecaria agallocha L.*, have emerged as promising anti-neuroinflammatory agents. These compounds exert their effects by inhibiting macrophage polarization and suppressing the activation of the NLRP3 inflammasome, highlighting their potential in mitigating neuroinflammation (113). Additionally, Thonningianin A (ThA) has demonstrated the ability to suppress NLRP3 inflammasome-driven inflammation and curb the overactivation of microglia and astrocytes through the induction of autophagy (114). Moreover, autophagy has been implicated in mitigating neuroinflammation in AD by modulating NLRP3 inflammasome activity (115). Consequently, targeting the autophagy-NLRP3 inflammasome axis using ThA holds potential as a novel therapeutic approach for AD (23). Additionally, research suggests that Eriodictyol exerts beneficial effects on AD by inhibiting NLRP3 activation. Eriodictyol can cross the BBB and significantly reduce the expression of NLRP3, caspase-1, and ASC proteins in brain tissue, while also decreasing the inflammatory cytokines IL-1β and IL-18. These effects improve cognitive function and memory (116), as well as attenuate AD pathology (23, 117). The ongoing phase 3 trial TRAILBLAZER-ALZ 2 (NCT04437511) (118), phase 2 clinical trial (NCT04795466) (81) and other AD clinical trials will offer a more comprehensive strategy for AD treatment (119) (Table 1).

5 Conclusion

The NLRP3 inflammasome plays a pivotal role in the pathogenesis of Alzheimer's disease by driving neuroinflammation, Aβ accumulation, tau pathology, and neuronal damage. Its activation is influenced by multiple factors, including ROS, mitochondrial dysfunction, and gut microbiota dysbiosis. Targeting the NLRP3 inflammasome through various therapeutic strategies, such as IL-1β modulation, natural compounds, and small-molecule inhibitors, offers promising potential to alleviate neuroinflammation and slow disease progression. Future research should focus on developing NLRP3-targeted therapies that can effectively cross the blood-brain barrier and provide long-term benefits in AD patients. Moreover, integrating biomarker identification and precision-targeted drug design into clinical research could expedite the transition from bench to bedside, ultimately offering earlier intervention and better protection against neurodegeneration in individuals at risk for or diagnosed with AD. By addressing the central role of the NLRP3 inflammasome in AD, these therapeutic approaches may pave the way for more effective treatments for this debilitating disease.

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