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Review

The Role of Pyroptosis in Alzheimer's Disease

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Abstract

Pyroptosis is a type of regulated cell death that relies on caspases, vesicles, and the cleavage of gasdermin proteins (which create pores in the cell membrane). The nucleotide-binding oligomerization domain-like receptor protein 3 (*NLRP3*) inflammasome, which is involved in this process, is the most widely studied inflammasome. Caspase-1 activates pro-inflammatory cytokines, such as IL-1β and IL-18. Gasdermin D (*GSDMD*) is the most important executive protein. *GSDMD*, a substrate rather than an upstream protease, determines the occurrence of pyroptosis. Pyroptosis is essential for maintaining body homeostasis, but excessive or poorly regulated cell death can aggravate the inflammatory response. Undoubtedly, this will be an important direction for future research on Alzheimer's disease (AD). Here, we review recent research progress on the morphological characteristics, molecular mechanisms, and role of pyroptosis in the context of AD, thereby providing new directions for identifying potential disease biomarkers and treatment strategies for AD.

Keywords: Alzheimer's disease; gasdermin D; inflammasome; pyroptosis; therapy

1. Introduction

Alzheimer's disease (AD) is a disorder that causes people to gradually lose their memory and cognition. The pathophysiological process of AD is thought to begin years, or even decades, before symptoms arise [1]. Despite decades of research, our knowledge of AD pathogenesis remains unclear, and our ability to intervene via the prevention or treatment of dementia is still limited. There is still much we don't know about the molecular mechanisms that lead to AD, and this is important because it would help us develop more sensitive diagnostic markers and find new ways to treat the disease.

Pyroptosis is an inflammatory form of regulated cell death and a critical and necessary host-defense immune mechanism. Increasing evidence shows that dysfunctional pyroptosis participates in neurological disorders such as Parkinson's disease [2], amyotrophic lateral sclerosis [3], and Huntington's disease [4]. There are emerging evidences that the inflammatory responses in the central nervous system (CNS) may be a major cause and common feature of AD [5,6]. Pyroptosis is also involved in β-amyloid (Aβ) protein deposition and the hyperphosphorylation of tau [5,7]. Thus, pyroptosis is important to the development of neuropathological lesions in AD. In our review, we summarize the process of pyroptosis, particularly in AD, to better understand the pathogenesis of AD and provide a novel strategy for more effective prevention, diagnosis, and treatment measures for AD.

2. Overview of Pyroptosis

2.1 Morphological Characteristics of Pyroptosis

There are two main ways for cell death to occur: ordered (programmed-like, regulated) and nonordered (necrosis). To date, over 20 forms of regulated cell death have been identified and studied, including apoptosis, autophagy or autophagic death, pyroptosis, and ferroptosis, but they are not all equally well characterized. Studies have shown that substrates, rather than their upstream proteases, determine the nature of cell death. Because gasdermin family members are indispensable executors of pyroptosis, pyroptosis is also known as gasdermin-mediated regulated cell death [8,9].

Pyroptotic cells display DNA fragmentation, which can be detected by terminal deoxynucleotidyl transferase dUTP nick-end labeling, but at a lower intensity than apoptotic cells. Chromatin condensation also occurs in pyroptosis, but the nucleus remains intact. Furthermore, pyroptotic cells become annexin-V-positive because, in early membrane rupture, the inner leaflet of membrane is exposed to the outside [10,11]. During pyroptosis, the cell membrane breaks down to create small holes with a diameter of 11–24 nm; this causes increased cell permeability and the release of inflammatory cytokines, lactate dehydrogenase, and other intracellular substances. The small pores in the cell membrane cause the cell to lose its salt and water balance, and this causes it to swell. Finally, the cell membrane is destroyed, and the cellular contents are released into the extracellular environment. This causes the body's immune system to become active, drawing in more inflam-

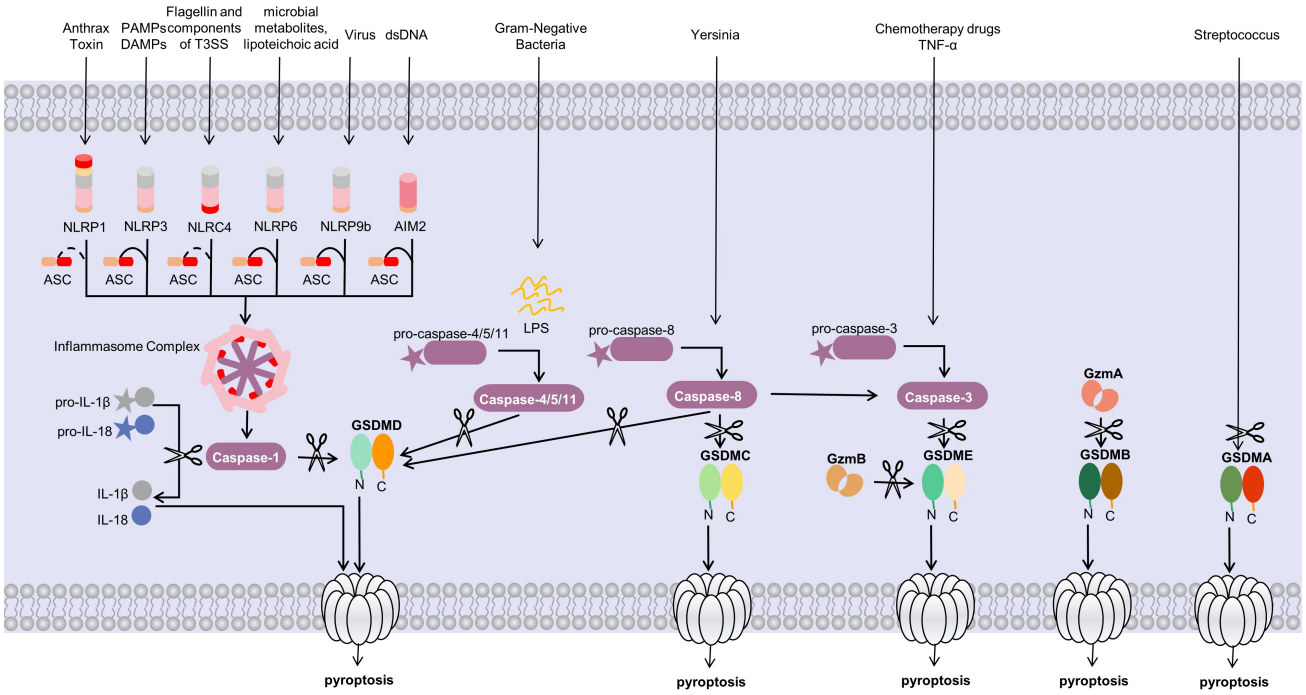

Fig. 1. Molecular mechanisms of pyroptosis. The canonical pyroptosis pathway depends on the inflammasome and *GSDMD* by caspase-1. Activated inflammasome promotes the activation of caspase-1, which cleaves the pore-forming factor *GSDMD*. Active caspase-1 also cleaves the proinflammatory cytokines such as IL-1β and IL-18. *NLRP1* initiates inflammasome activation upon anthrax toxin. *NLRP3* needs to be primed prior to activation. The activators of *NLRC4* are flagellin and components of T3SS, the adaptor protein ASC is not necessary for the assembly of *NLRC4* inflammasome. The activators of *NLRP6* are microbial metabolites and lipoteichoic acid. Rotavirus infection lead to the activation of *NLRP9b*. *AIM2* recognizes dsDNA in the cytosol. The non-canonical pyroptosis pathway requires directly binding of LPS to caspase-11 (murine) or caspase-4/-5 (human) and release of *GSDMD* N-terminus. Caspase-8 mediates the cleavage of *GSDMC* and *GSDMD*. Chemotherapy drugs and TNF-α promotes the activation of caspase-3, which cleaves the *GSDME*. Gzm B in NK cells and cytotoxic T lymphocytes can also directly cleave *GSDME*. Gzm A from cytotoxic lymphocytes could cleaves *GSDMB*. Human pathogen group A Streptococcus secretes SpeB, which induces *GSDMA*-dependent pyroptosis. DAMP, damage-associated molecular pattern; PAMP, pathogenassociated molecular patterns; ASC, apoptosis associated speck-like protein containing a caspase recruitment domain; LPS, lipopolysaccharide; GSDM, Gasdermin.

matory cells, and inducing a serious inflammatory reaction [12,13]. Unlike necrosis, pyroptotic cell death and the consequent inflammatory responses are reversible and controllable. Thus, pyroptosis has attracted increasing attention in the study of infectious diseases, various neoplastic diseases and metabolic diseases, and represents a new research direction.

2.2 Gasdermins in Pyroptosis

Members of the gasdermin family have been recently identified as having pore-forming activity and are found in many different cells and tissues. Currently, this family comprises six homologous genes in humans: gasdermin A (*GSDMA*); *GSDMB*; *GSDMC*; *GSDMD*; *GSDME*; and pejvakin. All gasdermins except for pejvakin contain a cytotoxic N-terminal ($GSDM^{NT}$) domain and a C-terminal ($GSDM^{CT}$) repressor domain. The $GSDM^{NT}$ fragment has the ability to form pores in the cell membrane, which can disrupt its integrity. The expression of $GSDM^{NT}$ alone can induce pyroptosis [8,14,15]. The $GSDM^{CT}$ fragment can bind to the $GSDM^{NT}$ domain and act as a repressor, whereas overexpression of $GSDM^{CT}$ can block cell death [8].

Pore formation by the gasdermin family is a characteristic of pyroptosis [16,17], the binding of the $GSDM^{NT}$ domain to membrane lipids causes it to change shape, which leads to the formation of pores. Experimental evidence indicates that the $GSDM^{NT}$ domain can directly interact with lipid molecules in cells. The $GSDMD^{NT}$ domain preferentially targets acidic phospholipids such as phosphoinositides and cardiolipin [18–21]. The N-terminal domains of other gasdermins, such as *GSDME* and *GSDMA*, have a similar way of forming small holes in the cell membrane [18].

At present, the mechanism by which *GSDMD* induces pore formation in the membrane (which constitutes

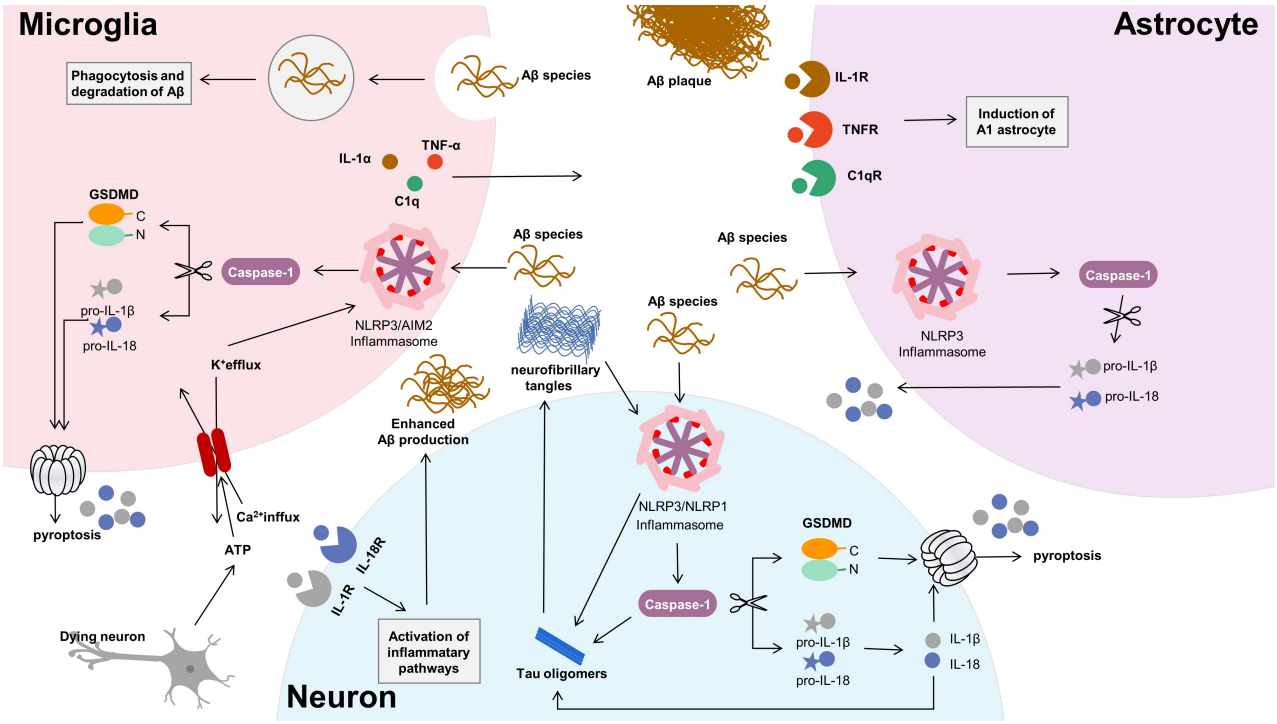

Fig. 2. Neuron-glia crosstalk in Alzheimer's disease. Microglia, working as both phagocytic cells and innate immunocyte, can recognize and clear Aβ. However, in AD, the canonical pyroptosis pathway is activated in Aβ-induced reactive microglia. Meanwhile, Aβ species can also induce pyroptosis in neurons. Activate *NLRP3*, caspase-1 and downstream IL-1β, IL-18 promote the aggregation of hyperphosphorylated tau, neurofibrillary tangles in turn trigger the activation of *NLRP3* inflammasome. The interaction between *NLRP3* and hyperphosphorylated tau promotes neuroinflammation and neuronal injury. Activated microglia induces A1 astrocytes by secreting IL-1α, TNF-α and C1q, and Aβ species induce the activation of *NLRP3* infammasome and caspase-1 in astrocytes, which futher triggering the release of IL-1β and IL-18.

cell pyroptosis) is relatively clear, but it is still a matter of debate how caspases recognize and cleave *GSDMD*. In studies on apoptosis, caspases have been shown to activate the substrate protein by recognizing a tetrapeptide sequence in the substrate and cleaving after the aspartate residue [22,23]. However, this process is different in pyroptosis. Recently, it was found that autocleavage at the Asp289/Asp285 location in caspase-4/11 creates p10. To carry out a tetrapeptide sequence-independent cleavage, the p10-form promotes the binding of caspase-4/11 to the $GSDMD^{CT}$ domain; caspase-1 employs a similar structural mechanism for targeting *GSDMD* [24].

2.3 Molecular Mechanisms of Pyroptosis

2.3.1 Regulatory Mechanism of Canonical Pyroptosis

The canonical pyroptosis pathway is mediated by caspase-1. Proteins called pattern recognition receptors (PRRs) assist the body in recognizing two groups of substances: damage-associated molecular patterns (DAMPs), which are linked to cell components, and pathogen-associated molecular patterns (PAMPs), which are linked to microbial infections. Inflammatory signaling cascades are thereby initiated. Several families of PRRs, including NOD-like receptors (NLRs), toll-like receptors (TLRs), and RIG-I-like receptors, play vital roles in the immune system [25]. The inflammasome is activated by various stimuli, which induces the activation of caspase-1. On the one hand, *GSDMD* which is cleaved and activated by activate caspase-1 causes cell membrane to form pores, and lead to pyroptosis; on the other hand, caspase-1 can rapidly process pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into their active proinflammatory cytokines, while IL-1 and IL-18 flow out of the pores and trigger inflammation [26] (Fig. 1).

A collection of multiprotein signaling complexes called inflammasomes are found in the cytoplasm. Several inflammasomes, including *NLRP1*, *NLRP2*, *NLRP3*, *AIM2*, and *NLRC4*, have been discovered [27]. The immune receptor protein *NLRP3*, adaptor protein ASC (apoptosis associated speck-like protein containing a caspase recruitment domain), and inflammatory protease caspase-1 make up the most extensively studied inflammasome, which reacts to microbial infections, endogenous danger signals, metabolic risk factors, and environmental stimuli [28,29]. An earlier investigation revealed that the gene expression of *NLRP3* was so low that it was insufficient to activate the assembly of an inflammasome during resting conditions. Therefore, the canonical *NLRP3* inflammasome is activated when two steps are completed [30–32]: the first step is the

Table 1. Studies on pyroptosis in CNS cell types in AD.

Experimental model	Cellular location	Comments	Reference
AD mice	microglia	Activation of *NLRP3*-caspase-1-*GSDMD* axis by ASC-Aβ composites	[44]
AD mice	astrocytes	Activation of *NLRP3* and caspase-1 by Aβ_{1-42}, but *GSDMD* was not detected	[45]
AD rats and PC12 cells	neurons	Activation of *NLRP1*-caspase-1-*GSDMD* axis by hyperphosphorylated tau	[7]
AD mice	neurons	Activation of *NLRP3*-caspase-1-*GSDMD* axis by Aβ_{1-42}	[5]
AD mice	neurons	Activation of *NLRP1*-caspase-1-*GSDMD* axis by Aβ	[46]
AD mice	oligodendrocytes	Activation of *NLRP3*-caspase-1-*GSDMD* axis by Aβ_{1-42}	[47]

priming step, through the myd88-NF-κB pathway, the ligands of TLRs, NLRs, and cytokine receptors cause the production of pro-IL-1 and *NLRP3* [33–35]. The second step is the activation step, which happens when a variety of foreign objects (PAMPs or DAMPs) cause *NLRP3* inflammasome to assemble and activate [36].

2.3.2 Regulatory Mechanism of Noncanonical Pyroptosis

The noncanonical pyroptosis pathway is mediated by caspase-4/5/11. Bacterial lipopolysaccharide stimulates and activates caspase family proteases (caspase-4/5 in humans and caspase-11 in mice), and activate caspase-4/5/11 cleaves *GSDMD*, which forms pores in the cell membrane and eventually leads to pyroptosis [14,37]. Unlike the canonical signaling pathway, IL-1α and high mobility group box 1, not IL-1β or IL-18, are released by caspase-4/5/11-mediated pyroptosis. Caspase-4/5/11 activates the transmembrane channel pannexin-1, causing an efflux of cellular ATP, which promotes P2X7 receptor-dependent pyroptosis [38]; the activation of pannexin-1 channels causes potassium efflux, which is essential for the activation of *NLRP3* inflammasome. Therefore, noncanonical pyroptosis can also induce an inflammatory cascade.

2.3.3 Other Caspase-Induced Pyroptosis

In addition to the two different pyroptosis pathways described above, recent research has revealed some new mechanisms. *GSDME* is specifically cleaved by caspase-3, and thereby induces the switching of caspase-3-mediated apoptosis to pyroptosis [39]. Caspases-3/7 which are thought to play a role in apoptosis, could induce *GSDMD*-associated microglial pyroptosis under neuroinflammatory conditions [40]. Caspase-8 is a caspase that is involved in apoptosis and necroptosis, however, recent evidence suggests that caspase-8 plays a critical role in pyroptosis [41]. The RIPK1- and caspase-8-dependent cleavage of *GSDMD* results in cell death; no other caspase is involved in the whole process [42]. Additionally, the lysosomal Ragulator-Rag complex initiates caspase-8-mediated pyroptosis by Yersinia [43].

3. Pyroptosis in CNS cell types

Pyroptosis has been assessed in the CNS using a variety of assays; here, we review the evidence for pyroptosis in each CNS cell type (Fig. 2; Table 1, Ref. [5,7,44–47]).

3.1 Microglia

Microglia is a type of resident macrophage present in the CNS. But the mechanism by which it works in the resting state is still poorly understood. Activated microglia can not only promote the repair of tissue damage, but also promote the inflammatory response of the CNS. However, the effect of inflammatory microglia on brain injury and damage is closely related to the pathogenesis of AD [6,48]. The *NLRP1*, *NLRP3*, and *AIM2* inflammasomes have been reported to be activated in microglia, astrocytes, and neurons [49–51], and the *NLRP3* inflammasome is highly activated in microglia [52]. Activation of the *NLRP3* inflammasome triggers the release of several proinflammatory cytokines, including IL-1β and IL18. Importantly, studies on microglia have shown that gasdermins are recognized and cleaved by caspases, leading to cellular swelling, membrane rupture, and other features of pyroptosis [44,53–58].

3.2 Astrocytes

Astrocytes are the most widely distributed in the brain and play an important role in normal central activities. Studies have shown that astrocytes play an important role in the inflammatory response of the CNS. Together with other glial cells (e.g., microglia, oligodendrocytes), astrocytes compose and maintain a regulated microenvironment [59,60]. Their activation states vary, ranging from neuroprotective (decreases inflammatory response, promotes repair) to neurotoxic (intensifies inflammatory response, causing neurodegeneration) [61]. Aβ and extracellular ATP, which are capable of activating LPS-induced astrocytes and interacting with the *NLRP3* inflammasome, create a neuroinflammatory environment by the excessive production and release of proinflammatory cytokines and promote pyroptosis in astrocytes *in vitro* and *in vivo* [45,62–64]. However, inconsistent results have been reported in studies with human astrocytes [65]; astrocytes in the brain exhibited *NLRP3*, cleaved *GSDMD* and strong caspase-8 immunoreactivity, but not ASC, caspase-1, or IL-18 [66].

3.3 Neurons

Pyroptosis is of great significance for the pathogenesis of AD. However, most studies have focused on glial cells, and there have been few experiments on the interaction between neurons and pyroptosis. The latest research suggests that pyroptosis is not restricted to glial cells; neu-

rons are immunoreactive to cleaved *GSDMD* [66]. Studies have showed that the inflammasomes of *NLRP3* and *NLRP1* may induce neuroinflammatory processes by pyroptosis in neurons. Aβ_{1-42} can induce pyroptosis via the *GSDMD* protein in neurons, and *NLRP3*/caspase-1 signaling is important for mediating *GSDMD* cleavage [5,67]. Tan and colleagues [46] have showed that the *NLRP1* inflammasome drives neuronal pyroptosis in AD mice, suggesting that *NLRP1*/caspase-1 signaling is a key pathways responsible for Aβ neurotoxicity. In addition, one study demonstrated that hyperphosphorylated tau could induce pyroptosis in PC12 cells, the release of IL-1β and IL-18 in turn increased hyperphosphorylated tau while spreading neuroinflammation [7].

3.4 Oligodendrocytes

Oligodendrocytes (OLs) are important for the functioning of the CNS. Although there is increasing evidence that OL damage and white matter degeneration are important pathological changes in AD, their roles in the occurrence and development of AD are still unclear [68]. Zhang *et al*. [47] reported that mature OLs in both AD patients and AD mice undergo *NLRP3*-dependent *GSDMD*-associated inflammatory injury, accompanied by demyelination and neurodegeneration. In mature OLs, overactivation of Drp1 leads to impaired glucose metabolism, leading to *NLRP3*-related inflammation and pyroptosis.

4. Association between Pyroptosis and AD

AD is a neurodegenerative disorder clinically defined by gradually increasing cognitive impairment and alterations in executive functions. The neuropathological hallmarks of AD are the accumulation of Aβ and neurofibrillary tau tangles (NFTs) [69]. Studies have confirmed that the inflammatory response mediated by inflammasomes play a key role in AD pathology. Rui *et al*. [70] have shown that *GSDMD*-mediated inflammasomes and pyroptosis were activated in peripheral blood mononuclear cells of patients with amnesiac mild cognitive impairment and AD. However, the interaction between pyroptosis and the pathophysiology of AD is not clear yet. Here, we summarize the relationship between pyroptosis and AD, focusing on Aβ plaques and NFTs.

4.1 Aβ

Activation of the *NLRP3* inflammasome by fibrillar Aβ and soluble Aβ has been described previously [71,72]. Heneka *et al*. [28,73] demonstrated that AD mice exhibit obvious inflammatory phenotypes in the cerebral cortex and hippocampus. It was characterized by the activation of microglia associated with Aβ plaques, accompanied by extensive vascular endothelial damage. *NLRP3*–/– or caspase-1–/– mice, mainly due to reduced activation of caspase-1 and IL-1β in the brain, increased Aβ content, thereby attenuating the loss of spatial memory and other AD symptoms [28,73]. In addition, in 5 xFAD mice aged 7–8 months, whose brains contained the ASC+/– genotype, the amyloid content in the brain was significantly reduced; inhibition of inflammasome activation enhanced phagocytosis capability of astrocytes and improves learning and memory [74]. Han *et al*. [5] found that Aβ_{1-42} can cause pyroptosis through *GSDMD* protein, and the *NLRP3*-Caspase-1 signaling pathway is the key to mediate *GSDMD* cleavage. The role of the *NLRP3* inflammasome in AD has also been confirmed in clinical research [75]. Aβ triggers the activation of inflammasomes and mediates pyroptosis in the brain; conversely, pyroptosis also accelerates the formation of neuritic plaques and is crucial for the development of AD.

4.2 Tau

Pyroptosis has been reported to act as a component in the progression of AD by its interaction with Aβ, but does pyroptosis affect tau pathology? Data on the correlation between tau hyperphosphorylation and pyroptosis are scarce. Previous studies have showed that the overexpression of proinflammatory cytokines increases neurofibrillary tangles [76], but recent studies have found that this phenomenon is caused by activation of the *NLRP3* inflammasome and pyroptosis. Inhibition of the *NLRP3* inflammasome reduced neurofibrillary tangles and significantly improved memory and cognition in AD mouse models [77]. Li *et al*. [7] used two hyperphosphorylated tau rat models and PC12 cells to study the correlation between tau protein and pyroptosis. The authors found that the high level of hyperphosphorylated tau induce the release of caspase-1, IL-1β and IL-18, and the degree of cell injury [7]. However, in AD brain tissues, *GSDMD*-positive neurons had no NFTs, but were found in close proximity to Aβ plaques [66].

5. Anti-Pyroptotic Therapies

With continuing research on pyroptosis, increasing evidence shows that pyroptosis can be used as a new therapeutic target for the treatment of AD (e.g., using *NLRP3* inflammasome inhibitors such as MCC950 and JC-124 [78,79] and proinflammatory caspase inhibitors such as VX765) [80,81]. However, none of them have been applied in the clinic. At present, there is no relevant report on *GSDMD* inhibitors as an AD treatment strategy. However, because *GSDMD* is the main executor of cell pyroptosis, it is reasonable to speculate that inhibitors of *GSDMD* might have a place in the treatment of AD.

In recent years, Traditional Chinese Medicine (TCM) has been widely used to treat AD, and research on the anti-pyroptotic effects of the active ingredients of TCM preparations has gained increasing attention. Because it inhibits NF-κB activity and NALP3 inflammasome activation, artemisinin has protective effects on the pathology of AD [82]. Dl-3-n-butylphthalide, also known as apigenin, suppresses the *TXNIP-NLRP3* interaction, inhibits *NLRP3* inflammasome activation, reduces proinflammatory cytokine levels, and prevents Aβ production [83].

Resveratrol has protective effects on AD pathology through suppressing the inflammatory response [84]. Treatment with Ginkgo biloba extract EGb 761 has been found to decrease microglial secretion of TNF-α and IL-1β, *NLRP3* and caspase-1, and inhibit inflammatory activation, thereby significantly improving cognitive function in mice [85]. Recent findings suggest that scutellarin inhibits neuroinflammation and microglial activation via regulation of the reactive oxygen species/*NLRP3* signaling pathway [86]. Scutellarin may be regarded as a caspase-11 inhibitor that inhibits the generation of $GSDMD^{NT}$, leading to reduced pyroptosis [87]. Ginsenoside, triptolide, epigallocatechin-3-gallate, curcumin, andrographolide, gastrodin, and the combination of Panax ginseng and Angelica sinensis, all have effect on inhibiting pyroptosis and alleviating the inflammatory response [88–95]. However, the therapeutic effects of these medications on alleviating pyroptosis in AD have not yet been reported.

Despite the substantial research effort focused on finding drugs for the treatment of AD, some therapeutics are single-target drugs, and most of these clinical trials have ended in failure. Therefore, a new approach to developing AD drugs is urgently needed. Considering the complex multifactorial etiology of AD, TCMs, which have the synergistic effects of binding multiple targets and activating multiple pathways, may be safe and ideal candidates as therapies for AD. Therefore, TCMs have broad application prospects in the treatment of AD.

6. Conclusions

All in all, Pyroptosis plays a pivotal role in the progression of AD. Our review highlights key developments in understanding pyroptosis in different CNS cells and AD pathology. Although the pyroptotic machinery has been studied in great detail, it is still a novel research topic, and there are many gaps and challenges in the regulatory mechanisms of pyroptosis during the AD process that should be investigated in future studies. In this review, we considered several critical points, including key pyroptosis-associated regulatory genes, noncoding RNAs, and even results from multiomics analyses. Perhaps pyroptosis-related molecules, such as *GSDMD*, can be used as biomarkers for diagnosis and prognosis. The exact pathogenetic mechanisms underlying AD remain uncertain, as there are still no drugs that can slow the progression of AD, let alone offer a cure. The exploration of pyroptosis may lead to new ways to treat AD. Overall, pyroptosis is a new perspective on the pathogenesis of AD.

Abbreviations

AD, Alzheimer's disease; CNS, central nervous system; Aβ, β-amyloid protein; NFTs, neurofibrillary tau tangles; NOD, nucleotide-binding oligomerization domain; IL, interleukin; OL, oligodendrocyte; TCM, traditional Chinese medicine.

Author Contributions

YJ and QZ designed the review. YJ, LZ and SL collected the data. YJ and QZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Jack CR, Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, *et al*. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 2018; 14: 535–562.

[2] Wang S, Yuan YH, Chen NH, Wang HB. The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in Parkinson's disease. International Immunopharmacology. 2019; 67: 458–464.

[3] Van Schoor E, Ospitalieri S, Moonen S, Tomé SO, Ronisz A, Ok O, *et al*. Increased pyroptosis activation in white matter microglia is associated with neuronal loss in ALS motor cortex. Acta Neuropathologica. 2022; 144: 393–411.

[4] Paldino E, D'Angelo V, Laurenti D, Angeloni C, Sancesario G, Fusco FR. Modulation of Inflammasome and Pyroptosis by Olaparib, a PARP-1 Inhibitor, in the R6/2 Mouse Model of Huntington's Disease. Cells. 2020; 9: 2286.

[5] Han C, Yang Y, Guan Q, Zhang X, Shen H, Sheng Y, *et al*. New mechanism of nerve injury in Alzheimer's disease: β-amyloid-induced neuronal pyroptosis. Journal of Cellular and Molecular Medicine. 2020; 24: 8078–8090.

[6] Hammond TR, Marsh SE, Stevens B. Immune Signaling in Neurodegeneration. Immunity. 2019; 50: 955–974.

[7] Li Y, Xu P, Shan J, Sun W, Ji X, Chi T, *et al*. Interaction between hyperphosphorylated tau and pyroptosis in forskolin and streptozotocin induced AD models. Biomedicine & Pharmacotherapy. 2020; 121: 109618.

[8] Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, *et al*. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 2015; 526: 660–665.

[9] Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, *et al*. Inflammatory caspases are innate immune receptors for intracellular LPS. Nature. 2014; 514: 187–192.

[10] Jorgensen I, Rayamajhi M, Miao EA. Programmed cell death as a defence against infection. Nature Reviews. Immunology. 2017; 17: 151–164.

[11] Siegel RM. Caspases at the crossroads of immune-cell life and death. Nature Reviews. Immunology. 2006; 6: 308–317.
[12] Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nature Reviews. Microbiology. 2009; 7: 99–109.
[13] He Y, Amer AO. Microbial modulation of host apoptosis and pyroptosis. Frontiers in Cellular and Infection Microbiology. 2014; 4: 83.
[14] Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, *et al*. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature. 2015; 526: 666–671.
[15] He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, *et al*. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Research. 2015; 25: 1285–1298.
[16] Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, *et al*. Non-canonical inflammasome activation targets caspase-11. Nature. 2011; 479: 117–121.
[17] Rühl S, Broz P. Caspase-11 activates a canonical NLRP3 inflammasome by promoting K(+) efflux. European Journal of Immunology. 2015; 45: 2927–2936.
[18] Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nature Reviews. Immunology. 2016; 16: 407–420.
[19] Broz P. Immunology: Caspase target drives pyroptosis. Nature. 2015; 526: 642–643.
[20] Ding J, Wang K, Liu W, She Y, Sun Q, Shi J, *et al*. Pore-forming activity and structural autoinhibition of the gasdermin family. Nature. 2016; 535: 111–116.
[21] Panganiban RA, Sun M, Dahlin A, Park HR, Kan M, Himes BE, *et al*. A functional splice variant associated with decreased asthma risk abolishes the ability of gasdermin B to induce epithelial cell pyroptosis. The Journal of Allergy and Clinical Immunology. 2018; 142: 1469–1478.e2.
[22] Crawford ED, Wells JA. Caspase substrates and cellular remodeling. Annual Review of Biochemistry. 2011; 80: 1055–1087.
[23] Poreba M, Strózyk A, Salvesen GS, Drag M. Caspase substrates and inhibitors. Cold Spring Harbor Perspectives in Biology. 2013; 5: a008680.
[24] Wang K, Sun Q, Zhong X, Zeng M, Zeng H, Shi X, *et al*. Structural Mechanism for GSDMD Targeting by Autoprocessed Caspases in Pyroptosis. Cell. 2020; 180: 941–955.e20.
[25] Brubaker SW, Bonham KS, Zanoni I, Kagan JC. Innate immune pattern recognition: a cell biological perspective. Annual Review of Immunology. 2015; 33: 257–290.
[26] Doitsh G, Galloway NLK, Geng X, Yang Z, Monroe KM, Zepeda O, *et al*. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature. 2014; 505: 509–514.
[27] Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature. 2012; 481: 278–286.
[28] Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. Nature Reviews. Neuroscience. 2018; 19: 610–621.
[29] Gross O, Poeck H, Bscheider M, Dostert C, Hannesschläger N, Endres S, *et al*. Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. Nature. 2009; 459: 433–436.
[30] Ozaki E, Campbell M, Doyle SL. Targeting the NLRP3 inflammasome in chronic inflammatory diseases: current perspectives. Journal of Inflammation Research. 2015; 8: 15–27.
[31] Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. Annals of the New York Academy of Sciences. 2014; 1319: 82–95.
[32] Zhong Z, Zhai Y, Liang S, Mori Y, Han R, Sutterwala FS, *et al*. TRPM2 links oxidative stress to NLRP3 inflammasome activation. Nature Communications. 2013; 4: 1611.
[33] Franchi L, Eigenbrod T, Muñoz-Planillo R, Ozkurede U, Kim YG, Arindam C, *et al*. Cytosolic double-stranded RNA activates the NLRP3 inflammasome via MAVS-induced membrane permeabilization and K+ efflux. Journal of Immunology. 2014; 193: 4214–4222.
[34] Franchi L, Kamada N, Nakamura Y, Burberry A, Kuffa P, Suzuki S, *et al*. NLRC4-driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. Nature Immunology. 2012; 13: 449–456.
[35] Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, *et al*. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. Journal of Immunology. 2009; 183: 787–791.
[36] Guo H, Callaway JB, Ting JPY. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nature Medicine. 2015; 21: 677–687.
[37] Kayagaki N, Wong MT, Stowe IB, Ramani SR, Gonzalez LC, Akashi-Takamura S, *et al*. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. Science. 2013; 341: 1246–1249.
[38] Yang D, He Y, Muñoz-Planillo R, Liu Q, Núñez G. Caspase-11 Requires the Pannexin-1 Channel and the Purinergic P2X7 Pore to Mediate Pyroptosis and Endotoxic Shock. Immunity. 2015; 43: 923–932.
[39] Wang Y, Gao W, Shi X, Ding J, Liu W, He H, *et al*. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. Nature. 2017; 547: 99–103.
[40] McKenzie BA, Fernandes JP, Doan MAL, Schmitt LM, Branton WG, Power C. Activation of the executioner caspases-3 and -7 promotes microglial pyroptosis in models of multiple sclerosis. Journal of Neuroinflammation. 2020; 17: 253.
[41] Fritsch M, Günther SD, Schwarzer R, Albert MC, Schorn F, Werthenbach JP, *et al*. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. Nature. 2019; 575: 683–687.
[42] Orning P, Weng D, Starheim K, Ratner D, Best Z, Lee B, *et al*. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. Science. 2018; 362: 1064–1069.
[43] Zheng Z, Deng W, Bai Y, Miao R, Mei S, Zhang Z, *et al*. The Lysosomal Rag-Ragulator Complex Licenses RIPK1 and Caspase-8-mediated Pyroptosis by *Yersinia*. Science. 2021; 372: eabg0269.
[44] Friker LL, Scheiblich H, Hochheiser IV, Brinkschulte R, Riedel D, Latz E, *et al*. β-Amyloid Clustering around ASC Fibrils Boosts Its Toxicity in Microglia. Cell Reports. 2020; 30: 3743–3754.e6.
[45] Ebrahimi T, Rust M, Kaiser SN, Slowik A, Beyer C, Koczulla AR, *et al*. α1-antitrypsin mitigates NLRP3-inflammasome activation in amyloid β_{1-42}-stimulated murine astrocytes. Journal of Neuroinflammation. 2018; 15: 282.
[46] Tan MS, Tan L, Jiang T, Zhu XC, Wang HF, Jia CD, *et al*. Amyloid-β induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease. Cell Death & Disease. 2014; 5: e1382.
[47] Zhang X, Wang R, Hu D, Sun X, Fujioka H, Lundberg K, *et al*. Oligodendroglial glycolytic stress triggers inflammasome activation and neuropathology in Alzheimer's disease. Science Advances. 2020; 6: eabb8680.
[48] Hashemiaghdam A, Mroczek M. Microglia heterogeneity and neurodegeneration: The emerging paradigm of the role of immunity in Alzheimer's disease. Journal of Neuroimmunology. 2020; 341: 577185.

[49] Lammert CR, Frost EL, Bellinger CE, Bolte AC, McKee CA, Hurt ME, *et al*. AIM2 inflammasome surveillance of DNA damage shapes neurodevelopment. Nature. 2020; 580: 647–652.
[50] Kaushal V, Dye R, Pakavathkumar P, Foveau B, Flores J, Hyman B, *et al*. Neuronal NLRP1 inflammasome activation of Caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated Caspase-6 activation. Cell Death and Differentiation. 2015; 22: 1676–1686.
[51] Zhou K, Shi L, Wang Y, Chen S, Zhang J. Recent Advances of the NLRP3 Inflammasome in Central Nervous System Disorders. Journal of Immunology Research. 2016; 2016: 9238290.
[52] Zhao G, Jiang K, Yang Y, Zhang T, Wu H, Shaukat A, *et al*. The Potential Therapeutic Role of miR-223 in Bovine Endometritis by Targeting the NLRP3 Inflammasome. Frontiers in Immunology. 2018; 9: 1916.
[53] Li S, Wu Y, Yang D, Wu C, Ma C, Liu X, *et al*. Gasdermin D in peripheral myeloid cells drives neuroinflammation in experimental autoimmune encephalomyelitis. The Journal of Experimental Medicine. 2019; 216: 2562–2581.
[54] Mamik MK, Power C. Inflammasomes in neurological diseases: emerging pathogenic and therapeutic concepts. Brain. 2017; 140: 2273–2285.
[55] Xu P, Zhang X, Liu Q, Xie Y, Shi X, Chen J, *et al*. Microglial TREM-1 receptor mediates neuroinflammatory injury via interaction with SYK in experimental ischemic stroke. Cell Death & Disease. 2019; 10: 555.
[56] Lee SW, de Rivero Vaccari JP, Truettner JS, Dietrich WD, Keane RW. The role of microglial inflammasome activation in pyroptotic cell death following penetrating traumatic brain injury. Journal of Neuroinflammation. 2019; 16: 27.
[57] Wang K, Sun Z, Ru J, Wang S, Huang L, Ruan L, *et al*. Ablation of GSDMD Improves Outcome of Ischemic Stroke Through Blocking Canonical and Non-canonical Inflammasomes Dependent Pyroptosis in Microglia. Frontiers in Neurology. 2020; 11: 577927.
[58] Yuan D, Guan S, Wang Z, Ni H, Ding D, Xu W, *et al*. HIF-1α aggravated traumatic brain injury by NLRP3 inflammasome-mediated pyroptosis and activation of microglia. Journal of Chemical Neuroanatomy. 2021; 116: 101994.
[59] Lin A, Liu J, Gong P, Chen Y, Zhang H, Zhang Y, *et al*. Serum amyloid A inhibits astrocyte migration via activating p38 MAPK. Journal of Neuroinflammation. 2020; 17: 254.
[60] Han X, Zhang T, Liu H, Mi Y, Gou X. Astrocyte Senescence and Alzheimer's Disease: A Review. Frontiers in Aging Neuroscience. 2020; 12: 148.
[61] Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, *et al*. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017; 541: 481–487.
[62] Zhu J, Hu Z, Han X, Wang D, Jiang Q, Ding J, *et al*. Dopamine D2 receptor restricts astrocytic NLRP3 inflammasome activation via enhancing the interaction of β-arrestin2 and NLRP3. Cell Death and Differentiation. 2018; 25: 2037–2049.
[63] Sun YB, Zhao H, Mu DL, Zhang W, Cui J, Wu L, *et al*. Dexmedetomidine inhibits astrocyte pyroptosis and subsequently protects the brain in in vitro and in vivo models of sepsis. Cell Death & Disease. 2019; 10: 167.
[64] Li L, Shu MQ, Chen J. CYLD deficiency exacerbates lipopolysaccharide (LPS)-induced pyroptosis in astrocytes of mice with sepsis. Biochemical and Biophysical Research Communications. 2019; 514: 1066–1073.
[65] Tarassishin L, Suh HS, Lee SC. LPS and IL-1 differentially activate mouse and human astrocytes: role of CD14. Glia. 2014; 62: 999–1013.
[66] Moonen S, Koper MJ, Van Schoor E, Schaeverbeke JM, Vandenberghe R, von Arnim CAF, *et al*. Pyroptosis in Alzheimer's disease: cell type-specific activation in microglia, astrocytes and neurons. Acta Neuropathologica. 2023; 145: 175–195.
[67] Bai Y, Liu D, Zhang H, Wang Y, Wang D, Cai H, *et al*. N-salicyloyl tryptamine derivatives as potential therapeutic agents for Alzheimer's disease with neuroprotective effects. Bioorganic Chemistry. 2021; 115: 105255.
[68] Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. Acta Neuropathologica Communications. 2018; 6: 22.
[69] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992; 256: 184–185.
[70] Rui W, Xiao H, Fan Y, Ma Z, Xiao M, Li S, *et al*. Systemic inflammasome activation and pyroptosis associate with the progression of amnestic mild cognitive impairment and Alzheimer's disease. Journal of Neuroinflammation. 2021; 18: 280.
[71] Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhelawon B, Carpenter SB, *et al*. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. Nature Immunology. 2013; 14: 812–820.
[72] Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, *et al*. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nature Immunology. 2008; 9: 857–865.
[73] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, *et al*. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013; 493: 674–678.
[74] Couturier J, Stancu IC, Schakman O, Pierrot N, Huaux F, Kienlen-Campard P, *et al*. Activation of phagocytic activity in astrocytes by reduced expression of the inflammasome component ASC and its implication in a mouse model of Alzheimer disease. Journal of Neuroinflammation. 2016; 13: 20.
[75] Saresella M, La Rosa F, Piancone F, Zoppis M, Marventano I, Calabrese E, *et al*. The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer's disease. Molecular Neurodegeneration. 2016; 11: 23.
[76] Ghosh S, Wu MD, Shaftel SS, Kyrkanides S, LaFerla FM, Olschowka JA, *et al*. Sustained interleukin-1β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model. Journal of Neuroscience. 2013; 33: 5053–5064.
[77] Ising C, Venegas C, Zhang S, Scheiblich H, Schmidt SV, Vieira-Saecker A, *et al*. NLRP3 inflammasome activation drives tau pathology. Nature. 2019; 575: 669–673.
[78] Dempsey C, Rubio Araiz A, Bryson KJ, Finucane O, Larkin C, Mills EL, *et al*. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. Brain, Behavior, and Immunity. 2017; 61: 306–316.
[79] Yin J, Zhao F, Chojnacki JE, Fulp J, Klein WL, Zhang S, *et al*. NLRP3 Inflammasome Inhibitor Ameliorates Amyloid Pathology in a Mouse Model of Alzheimer's Disease. Molecular Neurobiology. 2018; 55: 1977–1987.
[80] Flores J, Noël A, Foveau B, Beauchet O, LeBlanc AC. Pre-symptomatic Caspase-1 inhibitor delays cognitive decline in a mouse model of Alzheimer disease and aging. Nature Communications. 2020; 11: 4571.
[81] Flores J, Noël A, Foveau B, Lynham J, Lecrux C, LeBlanc AC. Caspase-1 inhibition alleviates cognitive impairment and neuropathology in an Alzheimer's disease mouse model. Nature Communications. 2018; 9: 3916.

[82] Shi JQ, Zhang CC, Sun XL, Cheng XX, Wang JB, Zhang YD, *et al*. Antimalarial drug artemisinin extenuates amyloidogenesis and neuroinflammation in APPswe/PS1dE9 transgenic mice via inhibition of nuclear factor-κB and NLRP3 inflammasome activation. CNS Neuroscience & Therapeutics. 2013; 19: 262–268.
[83] Wang CY, Xu Y, Wang X, Guo C, Wang T, Wang ZY. Dl-3-n-Butylphthalide Inhibits NLRP3 Inflammasome and Mitigates Alzheimer's-Like Pathology via Nrf2-TXNIP-TrX Axis. Antioxidants & Redox Signaling. 2019; 30: 1411–1431.
[84] Feng L, Zhang L. Resveratrol Suppresses Aβ-Induced Microglial Activation Through the TXNIP/TRX/NLRP3 Signaling Pathway. DNA and Cell Biology. 2019; 38: 874–879.
[85] Liu X, Hao W, Qin Y, Decker Y, Wang X, Burkart M, *et al*. Long-term treatment with Ginkgo biloba extract EGb 761 improves symptoms and pathology in a transgenic mouse model of Alzheimer's disease. Brain, Behavior, and Immunity. 2015; 46: 121–131.
[86] Bian HT, Wang GH, Huang JJ, Liang L, Xiao L, Wang HL. Scutellarin protects against lipopolysaccharide-induced behavioral deficits by inhibiting neuroinflammation and microglia activation in rats. International Immunopharmacology. 2020; 88: 106943.
[87] Ye J, Zeng B, Zhong M, Li H, Xu L, Shu J, *et al*. Scutellarin inhibits caspase-11 activation and pyroptosis in macrophages *via* regulating PKA signaling. Acta Pharmaceutica Sinica. B. 2021; 11: 112–126.
[88] Wang M, Wang R, Sun H, Sun G, Sun X. Ginsenoside Rb1 ameliorates cardiotoxicity triggered by aconitine via inhibiting calcium overload and pyroptosis. Phytomedicine. 2021; 83: 153468.
[89] Luo M, Yan D, Sun Q, Tao J, Xu L, Sun H, *et al*. Ginsenoside Rg1 attenuates cardiomyocyte apoptosis and inflammation via the TLR4/NF-kB/NLRP3 pathway. Journal of Cellular Biochemistry. 2020; 121: 2994–3004.
[90] Cai J, Yi M, Tan Y, Li X, Li G, Zeng Z, *et al*. Natural product triptolide induces GSDME-mediated pyroptosis in head and neck cancer through suppressing mitochondrial hexokinase-II. Journal of Experimental & Clinical Cancer Research: CR. 2021; 40: 190.
[91] Zhang C, Li X, Hu X, Xu Q, Zhang Y, Liu H, *et al*. Epigallocatechin-3-gallate prevents inflammation and diabetes -Induced glucose tolerance through inhibition of NLRP3 inflammasome activation. International Immunopharmacology. 2021; 93: 107412.
[92] Zheng Y, Zhang J, Zhao Y, Zhang Y, Zhang X, Guan J, *et al*. Curcumin protects against cognitive impairments in a rat model of chronic cerebral hypoperfusion combined with diabetes mellitus by suppressing neuroinflammation, apoptosis, and pyroptosis. International Immunopharmacology. 2021; 93: 107422.
[93] Li X, Wang T, Zhang D, Li H, Shen H, Ding X, *et al*. Andrographolide ameliorates intracerebral hemorrhage induced secondary brain injury by inhibiting neuroinflammation induction. Neuropharmacology. 2018; 141: 305–315.
[94] Ye T, Meng X, Zhai Y, Xie W, Wang R, Sun G, *et al*. Gastrodin Ameliorates Cognitive Dysfunction in Diabetes Rat Model via the Suppression of Endoplasmic Reticulum Stress and NLRP3 Inflammasome Activation. Frontiers in Pharmacology. 2018; 9: 1346.
[95] Hu J, Zeng C, Wei J, Duan F, Liu S, Zhao Y, *et al*. The combination of Panax ginseng and Angelica sinensis alleviates ischemia brain injury by suppressing NLRP3 inflammasome activation and microglial pyroptosis. Phytomedicine. 2020; 76: 153251.