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The P2X7R–NLRP3 inflammasome axis in Alzheimer's disease and therapeutic potential of synthetic and plant-derived natural compounds: A review

Rishabh Goswami¹, Nidhi Sharma¹, Vikas Jhawar¹, Rahul Singh¹, Poonam Ruhel², Dinesh K. Dhull¹✉¹Department of Pharmacy, School of Healthcare and Allied Sciences, GD Goenka University, Sohna–Gurugram, Haryana, India²Pharmacology Division, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India

ABSTRACT

Alzheimer's disease is a prevalent neurodegenerative disease that is characterized by synaptic dysfunction followed by neuronal loss. The core pathological mechanisms of Alzheimer's disease include the extracellular deposition of amyloid beta (A β) plaques and intracellular neurofibrillary tangle deposits inside the brain. These pathological hallmarks initiate the activation of neuro-immunological pathways that lead to neuronal loss. A β aggregation and neurofibrillary tangles function as danger signals and cause the release of extracellular adenosine-5'-triphosphate (ATP) from stressed or damaged neurons. The released ATP further amplifies the neuroinflammatory response by activating the P2X7 receptor (P2X7R) on microglial cells, which in turn facilitates NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome complex formation and activation. The latter event leads to caspase-1 activation-mediated release of cytokines, including interleukin-1 β and interleukin-18, followed by pyroptotic cell death. Consequently, this neuroinflammatory cascade results in cognitive impairment. Despite intensive research efforts, direct therapeutic targeting of the P2X7R has yielded limited clinical success, partly due to receptor compensatory mechanisms and genetic polymorphisms that affect treatment responsiveness. In this context, emerging evidence highlights the potential of targeting the downstream NLRP3 inflammasome *via* natural bioactive compounds or synthetic molecules as a more promising therapeutic strategy for modulating the neuroinflammatory pathways underlying Alzheimer's pathogenesis. Collectively, this review summarizes the progressive molecular events linking A β and tau pathology to neuroinflammation *via* the P2X7R-NLRP3 inflammasome axis, while underscoring the therapeutic potential of plant-derived bioactive compounds as well as synthetic molecules in mitigating the progression of Alzheimer's disease.

KEYWORDS: Alzheimer's disease; Neuroinflammation; Neurodegeneration; Neuroprotection; NLRP3; Purinergic; P2X7 receptor; Interleukin

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by progressive decline in cognitive performance, orientation, and reasoning skills. AD is more prevalent in people aged 65 and above; however, people younger than 65 can also develop AD. In the recent report, the population of Americans aged 65 and older is projected to grow from 65 million in 2026 to 82 million by 2050[1]. Familial AD, characterized by autosomal dominant inheritance, is rare, accounting for only about 1%–5% of all AD cases, and is associated with gene mutations such as *APP*, *PSEN1*, and *PSEN2*[2]. Conversely, sporadic AD (or sporadic late-onset AD) constitutes 95% or more of all cases and is influenced by multifactorial risk factors, such as aging, environmental factors, and genetic susceptibility[3]. Activation of the purinergic P2X7 receptor (P2X7R) in microglial cells plays an important role in AD, followed

✉To whom correspondence may be addressed. E-mail: dhulldinesh@gmail.com

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by activation of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasomes.

The histopathological hallmarks include accumulation of extracellular amyloid beta (A β) plaques and intracellular neurofibrillary tangle (NFT) formation. These pathological deposits cause microglia to transition from a quiescent to an activated phenotype, thereby resulting in massive proinflammatory cytokine release[4]. As a consequence, activation of a harmful downstream signaling cascade disrupts synaptic transmission, followed by degeneration of neuronal cells and finally neuronal loss[5]. A number of Food and Drug Administration (FDA)-approved drugs only alleviate symptoms and are incapable of curing the disease. Recently, the U.S. FDA has approved two disease-modifying therapies, lecanemab and donanemab, for the treatment of AD[6]. These medications exert therapeutic effects by targeting late-stage amyloid plaque deposits. Their FDA labeling includes a boxed warning for amyloid-related imaging abnormalities. This adverse event limits their clinical use. Therefore, it is imperative to develop early-stage therapies without unwanted side effects.

Microglia have been known to play a pivotal role in AD pathogenesis and disease progression[7]. These central immune cells get activated by pathological protein aggregates, such as A β and NFTs, and oxidative stress induced by free radicals such as superoxide and peroxynitrite. In addition, immune cells identify tissue damage by recognizing damage-associated molecular patterns (DAMPs), with adenosine 5'-triphosphate (ATP) serving as one classic DAMP member. The extracellular concentration of ATP is generally low in healthy tissue[8,9]; however, it increases at the site of cellular stress and injury, triggering the activation of the ionotropic P2X7R on the membrane of immune cells[10]. Recent studies indicate that DAMPs drive excessive inflammation, which facilitates the development of multiple diseases. Thus, targeting DAMPs or their receptor can have an advantage in preventing downstream signal activation.

P2X7R, an ion channel from the P2X family, has recently been identified as a significant factor in the pathogenesis of various neurodegenerative diseases[11]. This receptor is mainly expressed in central nervous system (CNS) immune cells, especially microglia, and regulates a number of cellular events like cellular activation, calcium signaling, cytokine release, and immune response. Microglia-driven inflammatory responses are influenced by multiple stimuli. Extracellular ATP-mediated P2X7R activation serves as a core signaling event in microglia by initiating the release of neurotropic factors and proinflammatory cytokines such as interleukin (IL)-1 β , IL-6, IL-18, and activation of NLRP3 inflammasomes[12]. As a sensor molecule, NLRP3 assembles with the adapter protein ASC and pro-caspase-1 to form the NLRP3 inflammasome, a critical protein complex of the innate immune

system. It facilitates the cleavage of cytokine precursors, leading to the generation of active IL-1 β and IL-18. Accumulating evidence has linked NLRP3 inflammasome activation to the progression of various neurodegenerative diseases, including AD. NLRP3 inflammasome has been observed to co-localize with neuritic plaques, and its level subsequently increases in the AD brain[13]. The activation of NLRP3 further promotes A β aggregation by reducing A β phagocytosis. However, its influence on AD pathogenesis is still not clear and needs to be explored.

Current therapeutic strategies for AD, including cholinesterase inhibitors, immunotherapy, gene therapy, modulation of A β and tau deposition, and anti-inflammatory or antioxidant approaches, largely manage symptoms without addressing the underlying disease mechanisms. This has intensified interest in agents capable of preventing or delaying disease progression, with neuroinflammation recognized as a central driver. Natural and synthetic compounds acting on the P2X7R–NLRP3 axis represent a promising and mechanistically targeted class of such agents. In this review, we present a classified overview of these natural and synthetic compounds, examining their roles in modulating P2X7R–NLRP3 signaling as a therapeutic strategy for AD.

2. Role of P2X7R

2.1. Role of P2X7R in cerebral physiology

Cerebral P2X7 plays a significant role in physiological activities, such as synaptic transmission, neurotransmitter release, and neuronal cell communication[14]. P2X7R has low ATP sensitivity across the P2X receptor family. Its activation generally requires ATP at high micromolar to millimolar concentrations (approximately two orders of magnitude higher than the majority of other P2X receptors). Meanwhile, basal extracellular ATP concentration in the healthy brain falls within the nanomolar range[15]. Because of its low sensitivity, the physiological concentration of extracellular ATP is usually too low to effectively activate P2X7R. A number of studies confirm that the basal extracellular ATP concentrations in healthy brain tissue are generally below the activation threshold of P2X7R. However, a focal ATP surge triggered by neuronal and glial activity enables physiological P2X7 signaling under normal conditions[16]. The effect persists till the ATP is degraded by ectonucleotidases. It is speculated that focal ATP concentration near the P2X7R may be markedly higher than ATP measured in extracellular fluid. Furthermore, higher extracellular ATP concentration due to cellular stress might trigger P2X7R-mediated NLRP3 signaling stimulation and subsequent inflammasome assembly[17].

2.2. Role of P2X7R in neuroinflammatory pathway of AD pathology

Neuroinflammation is widely acknowledged as a central contributor to the pathogenesis and progression of AD. Accumulating evidence suggests that persistent activation of innate immune signaling pathways within the CNS results in neuronal dysfunction, synaptic impairment, and progressive neurodegeneration[18]. Among purinergic signaling pathways, the ATP-gated P2X7R has attracted considerable attention because of its prominent role in regulating microglial activation and inflammasome-mediated inflammatory responses. P2X7R is predominantly expressed in microglia, although it could also be detected in astrocytes, neurons, and oligodendrocytes under both physiological and pathological conditions. Sustained activation of P2X7R has been implicated in multiple pathological processes relevant to AD, including neuroinflammation, oxidative stress, tau pathology, and synaptic dysfunction[19].

Activation of P2X7R induces microglial activation and stimulates the release of numerous pro-inflammatory mediators, including tumor necrosis factor- α (TNF- α), IL-6, IL-1 β , and IL-18, as well as various chemokines. ATP-dependent activation of P2X7R in

microglia promotes neuroinflammatory signaling and contributes to chronic inflammatory responses in neurodegenerative disorders. Experimental studies have shown that chronic administration of ATP or the potent P2X7 agonist dibenzoyl-ATP induces depression-like and neurobehavioral abnormalities, whereas genetic knockout or pharmacological inhibition of P2X7R reduces microglial activation and attenuates inflammatory injury in several CNS disease models[20,21]. Research has verified the neuroprotective effects of P2X7R antagonism in experimental models of ischemia-reperfusion injury, traumatic brain injury, sepsis-associated encephalopathy, and experimental autoimmune encephalomyelitis[22].

As one of the core pathological hallmarks of AD, A β peptides strongly interact with purinergic inflammatory signaling. P2X7R substantially modulates A β -induced microglial responses, and suppression of P2X7R expression enhances microglial phagocytosis and clearance of A β deposits[23]. Consequently, sustained P2X7R activation may impair microglial protective functions and facilitate amyloid pathological progression.

One of the most well-established downstream mechanisms of P2X7R is activation of the NLRP3 inflammasome (Figure 1). Upon ATP binding, P2X7R induces potassium efflux and ionic imbalance

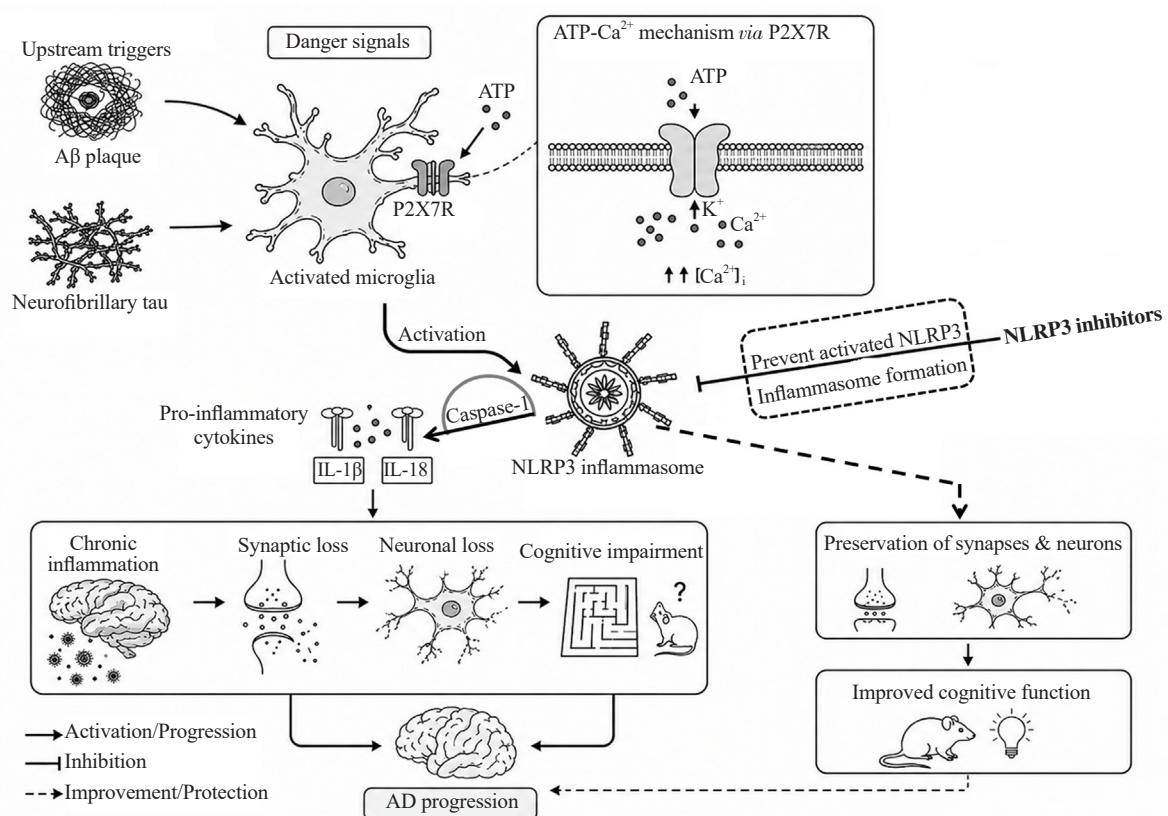


Figure 1. Role of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) modulators in Alzheimer's disease (AD) progression. A β : amyloid- β , P2X7R: P2X7 receptor, IL: interleukin.

that promote assembly of the NLRP3 inflammasome complex. Activated inflammasomes facilitate cleavage of pro-caspase-1 into active caspase-1, resulting in processing and release of mature IL-1 β and IL-18. This inflammatory axis plays a pivotal role in AD because A β aggregation, tau pathology, and DAMPs collectively drive inflammasome activation[13,24]. Sustained NLRP3 activation contributes to chronic neuroinflammation and progressive neuronal damage.

Further evidence underscores the importance of NLRP3 signaling in neurodegeneration. NLRP3 knockdown *via* NLRP3-targeted siRNA suppresses inflammasome activation, attenuates inflammatory cytokine release, and exerts neuroprotective effects[25,26]. These findings support the hypothesis that P2X7R–NLRP3 signaling serves as a therapeutic target for AD and other neurodegenerative disorders.

Mechanistically, P2X7R initially functions as a non-selective cation channel; however, prolonged stimulation leads to formation of larger membrane pores permeable to large molecules. This prolonged activation amplifies inflammatory signaling and facilitates downstream activation of mitogen-activated protein kinase pathways including p38, extracellular signal-regulated kinase, and c-Jun N-terminal kinase[27]. Activation of these pathways enhances production and secretion of pro-inflammatory cytokines, particularly TNF- α . Notably, P2X7R-triggered activation of c-Jun N-terminal kinase and p38 is mediated by Src family kinases and appears relatively independent of calcium influx[21].

P2X7R activation is also linked with oxidative stress. Increased calcium influx following receptor stimulation modulates mitochondrial function, activates NADPH oxidase, and promotes excessive reactive oxygen species (ROS) generation[28]. In AD, mitochondrial dysfunction and defects in electron transport chain activity further amplify ROS production, contributing to oxidative damage and neuronal vulnerability. Elevated oxidative stress also exacerbates synaptic dysfunction and accelerates disease progression[29].

P2X7R signaling has also been implicated in the regulation of tau pathology. Under physiological conditions, P2X7R participates in neuronal development, axonal growth, and neurite branching. However, sustained or aberrant receptor activation promotes neuroinflammatory and oxidative stress responses that can dysregulate intracellular kinase signaling pathways, including glycogen synthase kinase-3 β , a major tau kinase. Enhanced glycogen synthase kinase-3 β activity subsequently promotes tau hyperphosphorylation, facilitating tau aggregation and neurofibrillary pathology[30]. Hyperphosphorylated tau disrupts intracellular trafficking systems and contributes to neuronal susceptibility to oxidative damage and degeneration.

Synaptic dysfunction is another major consequence of P2X7R hyperactivation. Experimental studies on synaptosomes treated with ATP or dibenzoyl-ATP have demonstrated that P2X7R activation promotes glutamate release through a Ca²⁺-dependent pathway, thereby enhancing excitatory neurotransmission[31]. Excessive glutamate accumulation and ATP-mediated excitotoxicity may contribute to synaptic impairment during AD progression. Increased P2X7R activity associated with A β accumulation further aggravates oxidative stress and synaptic deterioration[32].

Microglia, the resident macrophages of the CNS, are pivotal for innate immune surveillance and maintenance of neuronal homeostasis. Under physiological homeostasis, microglia display a highly ramified morphology characterized by numerous motile processes that continuously survey the CNS microenvironment[33]. In response to pathological stimuli such as infection, injury, or protein aggregation, microglia undergo morphological transformation into activated amoeboid phenotypes characterized by enlarged somata, retracted processes, enhanced phagocytic activity, and increased production of inflammatory mediators[34]. Classically activated (M1-like) microglia predominantly produce pro-inflammatory cytokines, ROS, and reactive nitrogen species, driving neuroinflammation and neuronal injury. In contrast, alternatively activated (M2-like) microglia are associated with tissue repair, resolution of inflammation, and neuroprotection through the release of anti-inflammatory cytokines and trophic factors, including IL-4, IL-13, nerve growth factor, and fibroblast growth factor. Dysregulated polarization of microglia toward a pro-inflammatory M1-like phenotype has been implicated in the progression of AD, where sustained production of inflammatory cytokines, ROS, and other neurotoxic mediators contributes to synaptic dysfunction, neuronal injury, and the exacerbation of amyloid and tau pathology[18,35].

In addition to immune surveillance, microglia play a crucial role in synaptic pruning, a physiological process essential for the maturation, refinement, and maintenance of neuronal circuits. Through activity-dependent elimination of redundant or functionally weak synapses, microglia contribute to the establishment of functional neural networks throughout development and lifespan[7,36]. However, excessive activation of inflammatory pathways, particularly IL-1 β signaling, disrupts synaptic plasticity by impairing long-term potentiation and altering long-term depression. Sustained neuroinflammation can consequently promote pathological synaptic elimination, leading to synaptic dysfunction, cognitive impairment, and neurodegeneration[5,37]. Because IL-1 β is a major downstream product of P2X7R-mediated NLRP3 inflammasome activation, chronic activation of this pathway may contribute to impaired

long-term potentiation, aberrant synaptic pruning, and progressive neurodegeneration characteristic of AD.

Astrocytes are another important cellular component involved in P2X7R-mediated neuroinflammation[38]. Under physiological conditions, astrocytes play essential roles in maintaining CNS homeostasis by regulating synaptogenesis, neurotransmitter recycling, metabolic support, and neuronal survival. In AD, astrocytes undergo reactive transformation characterized by increased expression of glial fibrillary acidic protein and accumulation around A β plaques and NFTs[39]. Microglia are the primary source of inflammatory cytokines in the brain; reactive astrocytes substantially shape the chronic neuroinflammatory milieu by secreting pro-inflammatory mediators, including IL-1 β , IL-6, TNF- α , and various chemokines. These factors enhance glial crosstalk, disrupt neuronal function, and promote disease progression[40]. Furthermore, activation of astrocytic P2X7R induces oxidative stress *via* NADPH oxidase-dependent ROS generation, thereby exacerbating neuroinflammation, disrupting neuronal homeostasis, and facilitating neurodegeneration[41].

Oligodendrocytes and oligodendrocyte progenitor cells also express functional P2X7R[42]. Sustained activation of P2X7R induces excessive calcium influx and contributes to oligodendrocyte death, suggesting that ATP-mediated neurotoxicity

is not limited to neurons and microglia but also impairs white matter integrity. Pathological elevation in extracellular ATP levels is therefore implicated in demyelination and oligodendrocyte dysfunction under neurodegenerative conditions[43].

Accumulating evidence highlights P2X7R as a pivotal regulator of neuroinflammation in AD. By orchestrating microglial activation, inflammasome assembly, oxidative stress responses, and glia-mediated synaptic alterations, chronic P2X7R signaling drives a self-perpetuating inflammatory cascade that accelerates neurodegeneration. These findings establish P2X7R as a promising therapeutic target for interrupting pathogenic neuroimmune signaling and slowing disease progression.

3. Bioactive or synthetic molecules with NLRP3-mediated biological effects

A number of plant-derived bioactive agents or synthetic molecules have been reported to have NLRP3-mediated effects (Figure 2).

3.1. Natural compounds (Phytochemicals)

Dalbergin is a major bioactive isoflavonoid/phenolic constituent

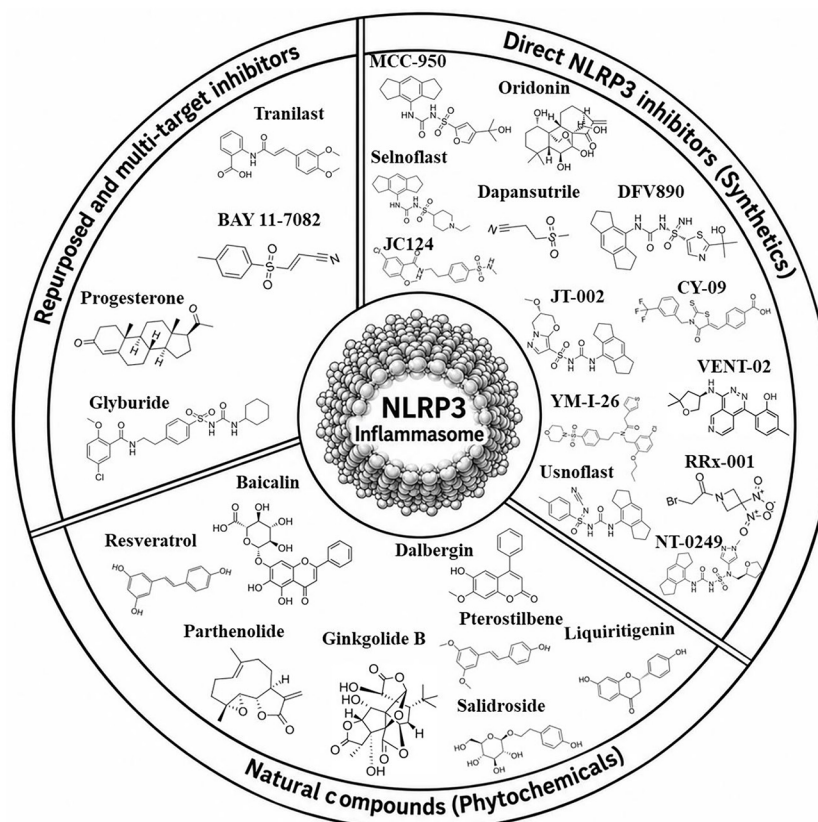


Figure 2. Three categories of NLRP3 inflammasome inhibitors.

isolated from the bark of *Dalbergia sissoo* (Fabaceae), and is traditionally used for its anti-inflammatory and antioxidant properties[44,45]. In preclinical models of neurodegeneration, it showed neuroprotective effects proposed to be mediated *via* modulation of the P2X7R–NLRP3 pathway[46–48]. However, the precise mechanisms underlying dalbergin's actions at the receptor or inflammasome level in AD models remain to be investigated.

Resveratrol is a natural polyphenolic stilbene predominantly found in grapes (*Vitis vinifera*), berries, and peanuts. Resveratrol modulates NLRP3 activity *via* upstream regulators such as P2X7 and NF- κ B, while activating antioxidant pathways. Despite rapid absorption, it exhibits poor bioavailability due to extensive first-pass metabolism (glucuronidation and sulfation)[49]. Despite considerable evidence for the neuroprotective effect of resveratrol, its clinical use is limited due to low aqueous solubility, poor chemical stability, and a short plasma half-life. The CNS penetration of resveratrol is modest and functionally relevant[50]. Preclinical evidence showed a neuroprotective effect of resveratrol *via* modulating the P2X7R/NLRP3 pathway[51,52].

Pterostilbene is a naturally occurring dimethylated analogue of resveratrol, primarily isolated from blueberries (*Vaccinium* spp.). Structural methylation confers enhanced lipophilicity, leading to improved oral bioavailability and metabolic stability compared to resveratrol. It demonstrates favourable tissue distribution, including CNS exposure, and a relatively longer half-life. It exerts a wide range of pharmacological effects by inhibiting NLRP3 inflammation activation, which is linked to suppression of inflammation and oxidative stress[53]. Li and co-workers showed that administration of pterostilbene attenuates the A β _{1–42}-induced microglial activation through NLRP3/caspase-1 pathway inhibition[54].

Baicalin is a flavone glycoside derived from the roots of *Scutellaria baicalensis*. It exhibits low oral bioavailability due to poor absorption and rapid metabolism; however, it is converted to its aglycone baicalein, which is more readily absorbed. Baicalin undergoes extensive first-pass glucuronidation, as reported in an animal study[55]. Substantial preclinical evidence showed its potential in the treatment of various neurological diseases[56,57]. The protective effect has been linked to the inhibition of NF- κ B-mediated activation of NLRP3 inflammasome and attenuation of ferroptosis[58,59].

Parthenolide, a sesquiterpene lactone isolated from *Tanacetum parthenium* (feverfew), exhibits protective effects in diabetic neuropathy, Huntington's disease, and cognitive impairment animal models[60–62]. Mechanistically, parthenolide interferes with upstream inflammatory pathways, including NF- κ B, thereby preventing NLRP3 inflammasome assembly and activation[63,64]. Molecular docking studies further demonstrate strong binding affinity toward NLRP3 (–8.3 kcal/mol)[64]. Pharmacokinetically, parthenolide displays moderate lipophilicity but limited aqueous solubility and bioavailability, while rapid metabolism and thiol reactivity may

restrict its systemic stability, prompting development of structurally optimized derivatives[65].

Salidroside, a phenylpropanoid glycoside isolated from *Rhodiola rosea*, demonstrated neuroprotective and anti-inflammatory activities in various neurological disease or disorder models such as Parkinson's disease, AD, depression, and autism spectrum disorder[66–69]. Further, its protective effect is thought to be due to modulation of the TXNIP/NLRP3 and P2X7/NF- κ B/NLRP3 signaling pathways[66,70]. Molecular docking and dynamics analyses demonstrate stable binding affinity toward NLRP3[71]. Pharmacokinetic studies indicate favourable aqueous solubility, rapid gastrointestinal absorption, and broad tissue distribution, including CNS penetration, although systemic elimination is relatively rapid with a short half-life in rodents (~1 h)[72,73].

A number of studies show the anti-inflammatory and neuroprotective effects of ginkgolide B. Ginkgolide B treatment prevents pathological processes by inhibiting NLRP3 signaling and by transforming microglial M1 to M2 phenotype[74]. However, its limited brain permeability restricts its clinical utility, highlighting the need for formulation strategies to enhance brain targeting.

Liquiritigenin and isoliquiritigenin are bioactive flavonoid derivatives isolated from *Glycyrrhiza glabra* (licorice). It has been reported that treatment with liquiritigenin showed neuroprotective effects through the attenuation of NLRP3 inflammasome activation by reducing caspase-1 expression and promoting microglial polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, as observed in both *in vitro* and *in vivo* models of AD[75]. In addition, isoliquiritigenin potently suppresses NLRP3 inflammasome activation independently of Toll-like receptor 4 (TLR4) inhibition, suggesting a direct modulatory effect on inflammasome signaling[76]. Pharmacokinetic studies indicate moderate oral absorption and predominant phase II metabolism *via* glucuronidation and sulfation[75,76].

3.2. Direct NLRP3 inhibitors (Synthetic)

MCC-950 (CRID3) is a synthetic diarylsulfonylurea derivative identified through inflammasome-targeted screening. MCC-950 is a direct inhibitor of the NLRP3 ATPase site (IC₅₀ = 7.5 nM) and its activity, thereby preventing inflammasome assembly[77]. Preclinical pharmacokinetic studies indicate good systemic exposure following oral administration, moderate plasma protein binding, and sufficient tissue distribution, including the CNS. MCC-950 has been found to reduce canonical and non-canonical activation of NLRP3 inflammasome in inflammatory responses[78,79]. However, clinical application has been limited due to hepatotoxicity concerns, which halted early-phase trials[80].

Oridonin acts as a direct covalent inhibitor of NLRP3 rather than merely modulating upstream NF- κ B inflammatory pathways. It

suppresses inflammasome activation by disrupting the NLRP3-NEK7 interaction through covalent binding to cysteine-279 within the NACHT domain of NLRP3[81].

JC124 is a synthetic small-molecule NLRP3 inflammasome inhibitor with demonstrated efficacy in experiments of neuroinflammatory disorders. Preclinical evidence suggests favorable CNS penetration and significant attenuation of neuroinflammation and oxidative stress, accompanied by improved behavioral and cognitive outcomes. In kainic acid-treated NLRP3 wild-type mice, JC124 markedly reduced seizure severity and depressive-like behaviour. The latter effects were absent in NLRP3 knockout mice, supporting an NLRP3-dependent mechanism[82]. In APP/PS1 transgenic mice, JC124 reduced A β burden and neuroinflammation while preserving synaptic plasticity, enhancing hippocampal neurogenesis, and improving cognitive performance[83].

Dapansutril (OLT1177) is a β -sulfonyl nitrile compound developed as a selective NLRP3 inhibitor. It is orally bioavailable, with favorable safety and tolerability, and is a specific inhibitor of the NLRP3 inflammasome[84]. Dapansutril has been shown to ameliorate immunological inflammatory conditions[85]. In another study, chronic oral administration of dapansutril at clinically relevant doses improved motor function that is linked to reduction in gliosis and synucleinopathy in mouse models[86,87].

VENT-02 is a novel, orally active, brain-penetrant NLRP3 inhibitor that is currently under phase II clinical investigation for the treatment of mild-to-moderate Parkinson's disease. It showed efficient CNS distribution and suppression of α -synuclein-associated neuroinflammation.

DFV890 is a selective small-molecule NLRP3 inhibitor developed for treating systemic inflammation. Clinical pharmacology studies report dose-dependent inhibition of IL-1 β release, with predictable exposure profiles and a favorable safety margin[88].

An investigational NLRP3 inhibitor, NT-0249, has been evaluated in preclinical models of inflammatory disease[89,90]. It demonstrates dose-dependent pharmacodynamic effects, though detailed pharmacokinetic characterization remains to be explored.

CY-09 is a synthetic small molecule that directly binds the Walker A motif within the NLRP3 NACHT domain, blocking ATP binding and thereby suppressing NLRP3 ATPase activity and inflammasome assembly[91]. CY-09 demonstrates high target selectivity, with no inhibitory effect on related sensors NLRP1, NLRC4, or NOD2, and has shown efficacy in preclinical models of gout, type 2 diabetes, and cryopyrin-associated periodic syndromes; however, dedicated evaluation in AD or broader neuroinflammatory models remains to be established.

JT002 is a novel small-molecule NLRP3 inhibitor developed for autoinflammatory disorders. JT002 potently reduces NLRP3-dependent proinflammatory cytokine production and prevents pyroptosis across multiple cellular assays, demonstrating oral

bioavailability and *in vivo* target engagement in preclinical models[92]. While its primary preclinical validation lies in peripheral inflammatory and autoimmune contexts, its mechanism of action supports potential extension to neuroinflammatory models.

YM-I-26 is an arylsulfonamide-based small-molecule NLRP3 inhibitor. It suppresses NLRP3-mediated IL-1 β and IL-18 release and enhances BV2 microglial phagocytosis of amyloid- β without cytotoxicity[93]. As an early-stage compound, further studies are needed to characterize *in vivo* efficacy, pharmacokinetics, and blood-brain barrier permeability of YM-I-26.

ZYIL-1 (Usnoflast) is an orally active, selective, small-molecule NLRP3 inflammasome inhibitor with an IC₅₀ value of 7 nM. ZYIL-1 has been shown to suppress lipopolysaccharide- and ATP-induced IL-1 β and IL-18 production *in vivo*, indicating potent inhibition of NLRP3 inflammasome activation[94]. Preclinical and clinical evidence has demonstrated a favorable safety, tolerability, and pharmacokinetic profile, along with neuroprotective potential across CNS diseases[95–97]. These findings support its promise as a candidate for translation into disease-modifying therapy for CNS disorders; however, further studies are required to validate this translational potential[98].

RRx-001 (Nirozetone) is a CNS-penetrant chimeric small molecule with a unique triple-action mechanism, functioning as an NLRP3 inflammasome inhibitor, Nrf2 pathway inducer, and nitric oxide superagonist[99]. In lipopolysaccharide-stimulated microglia, RRx-001 exerted protective effects by disrupting TLR4 pathway signaling and suppressing NLRP3 transcription[100]. Furthermore, RRx-001 attenuated the upregulated expression of lipocalin-2 and NLRP3 inflammasome activation in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease, thereby mitigating dopaminergic neuronal loss and motor deficits[101]. Rx-001 treatment has also been reported to show an improvement in learning and spatial memory performance in the 3xTg-AD mouse model[102]. Collectively, these findings suggest that RRx-001 may have therapeutic potential in neuroinflammation-driven neurodegenerative disorders.

Selnoflast (RO-7486967) is an orally active, selective, and reversible small-molecule NLRP3 inflammasome inhibitor. In a Phase 1b study of patients with moderate-to-severe ulcerative colitis, selnoflast demonstrated a favorable safety and tolerability profile, with an inhibitory effect on IL-1 β [103]. It has also been evaluated in patients with early-stage idiopathic Parkinson's disease in a Phase 1b trial[104]. However, its efficacy in NLRP3-associated AD pathology remains to be established.

3.3. Repurposed and multi-target inhibitors

BAY 11-7082 is a synthetic vinyl sulfone compound originally identified as an NF- κ B inhibitor and later recognized as a modulator of NLRP3 inflammasome activation. Mechanistically,

it suppresses inflammasome activity through inhibition of NLRP3 ATPase function, thereby impairing inflammasome assembly and downstream caspase-1 activation[105]. In experimental autoimmune encephalomyelitis models, BAY 11-7082 reduced NLRP3 inflammasome expression and associated neuroinflammation[106]. Similarly, in oxygen-glucose deprivation-induced BV-2 microglial cells, treatment with BAY 11-7082 significantly decreased NLRP3 and cleaved caspase-1 protein levels[107].

Glyburide (Glibenclamide) is a synthetic second-generation sulfonylurea and is widely used as an antidiabetic agent. Beyond its pancreatic K⁺/ATP channel activity, glyburide inhibits NLRP3 activation indirectly. It exhibits high oral bioavailability, extensive plasma protein binding (>95%), and hepatic metabolism (CYP2C9)[108]. CNS penetration is limited under physiological conditions, although disruption of the blood-brain barrier may enhance its central effects[109]. Preclinical studies showed that glyburide reduces neuroinflammation by inhibiting NLRP3 inflammasome[110]. In addition, administration of glyburide reduced the neuroinflammation by inhibiting microglial activation and neuroinflammatory cytokines such as IL-1 β , IL-6, and TNF- α [111].

Tranilast is a clinically used anti-allergic drug repurposed as a direct NLRP3 inhibitor. Tranilast binds NLRP3 directly, blocking its oligomerization and downstream inflammasome activation independently of ATPase inhibition, distinguishing its mechanism from CY-09 and related compounds[112]. Preclinical evidence showed a neuroprotective effect of tranilast in rodent models of ischemic stroke and streptozotocin-induced sporadic AD[113,114]. Further, its established human safety profile from prior clinical use offers a potential de-risking advantage for repurposing toward neuroinflammatory indications. However, further studies are warranted to establish its efficacy specifically in AD models and to substantiate its therapeutic potential in AD-associated neuroinflammation.

Progesterone is an endogenous neurosteroid with demonstrated anti-inflammatory and neuroprotective activity across multiple models of neurological injury and neuroinflammation. In A β -stimulated astrocytes, progesterone suppresses NLRP3-caspase-1 inflammasome activation by enhancing autophagy[115]. Beyond AD models, progesterone attenuates NLRP3 inflammasome activation and promotes autophagy following ischemic brain injury[116], suppresses TLR4/NLRP3 signaling in human microglia in the context of drug-resistant epilepsy[117], and reduces neuroinflammation-driven depressive-like behaviors in depression models[118,119]. It further induces an M1-to-M2 microglial phenotype switch while suppressing NLRP3 inflammasome activity in a cuprizone-induced demyelination model[120]. Collectively, this consistent cross-model suppression of NLRP3 signaling supports therapeutic potential of progesterone in neuroinflammation-mediated

neurological disease, though its therapeutic application requires careful consideration of its hormonal effects.

4. Challenges in clinical translation

Despite the robust preclinical evidence supporting the neuroprotective potential of targeting P2X7R and modulation of downstream NLRP3 signaling, the clinical translation of targeted therapies faces significant hurdles due to poor pharmacokinetic profiles and low systemic bioavailability of many potent compounds. Furthermore, achieving optimum blood-brain barrier penetration remains a critical bottleneck for treating neuroinflammatory disorders. While derivatives like pterostilbene offer improved lipophilicity and metabolic stability, other promising agents such as ginkgolide B are restricted by limited brain permeability. Another challenge is safety concerns, exemplified by the potent NLRP3 inhibitor MCC-950, which was paused in early-phase trials due to hepatotoxicity. Consequently, the field currently requires structural optimization and innovative formulation strategies to balance potent efficacy with the metabolic stability and safety margins necessary for successful clinical translation.

5. Conclusion

AD remains a major unmet medical challenge owing to its complex and multifactorial pathogenesis, which involves the interplay of neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic impairment, and protein aggregation. Among the emerging therapeutic targets, the purinergic P2X7R has gained considerable attention as a critical regulator of neuroimmune signaling and a key contributor to disease progression. Accumulating preclinical evidence indicates that aberrant P2X7R activation drives inflammatory and neurodegenerative cascades *via* downstream NLRP3 inflammasome assembly, thereby linking extracellular danger signals to neuronal dysfunction and cognitive decline. Consequently, modulation of the P2X7R-NLRP3 axis represents a promising strategy for disease modification in AD.

This review classifies P2X7R-NLRP3-targeting agents into three categories: natural modulators, synthetic NLRP3 inhibitors, and repurposed multi-target inhibitors. Natural compounds show antioxidant, anti-inflammatory, and neuroprotective activity by suppressing NF- κ B, MAPK, or NLRP3 activation. However, their poor pharmacokinetic profile, such as poor aqueous solubility, extensive first-pass metabolism, and modest CNS penetration, limits their clinical translation.

Synthetic inhibitors offer greater target specificity and, in several

cases, better CNS bioavailability, with some already in clinical evaluation. Repurposed agents further demonstrate the versatility of NLRP3 modulation across established drug classes, though blood-brain barrier penetration and off-target effects remain concerns for such candidates.

Collectively, the P2X7R-NLRP3 axis is considered to be a mechanistically coherent and druggable target for disease-modifying intervention in AD. However, advancement of candidates toward this target needs structure-activity optimization to enhance P2X7R selectivity, rigorous pharmacokinetic and blood-brain barrier profiling, and delivery strategies designed to improve CNS-directed translational value.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

RG contributed to conceptualization, investigation, methodology, writing the original draft, review, editing, and formal analysis. NS was involved in conceptualization, investigation, formal analysis, writing, review and editing. VJ and RS were engaged in critical review and editing of the manuscript, and formal analysis. PR contributed to data collection, revision of the manuscript, and visualization. DKD was responsible for conceptualization, design of the study, manuscript writing, review, editing, and supervision.

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