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Review Article

Inhibitors of NF-κB and P2X7/NLRP3/Caspase 1 pathway in microglia: Novel therapeutic opportunities in neuroinflammation induced early-stage Alzheimer's disease

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ABSTRACT

Microglial activation is a distinguished attribute in many neurodegenerative diseases of aging. Compelling evidence suggests that neuroinflammation stimulated by microglia, the resident macrophage-like immune cells in the brain, play a contributing role in the pathogenesis of Alzheimer's disease (AD). Postmortem brain tissue of individuals with AD has credibly demonstrated that neuroinflammation is likely to be a key driver of the disease. Recently, It has been found that manipulating β-amyloid directly is an impracticable approach for therapeutic intervention due to the failure of β-amyloid-lowering drugs in clinical trials. Further, Current treatments relieve only symptoms and modestly improve disease condition but do not reverse or prevent disease. Therefore, Inhibition of microglia activation is effective strategies against the multifactorial and complex AD. More recently there has been a center of attention on converting microglia from this classic state to an alternate state in which the noxious effects are reduced and their phagocytic action toward Aβ improved. The nuclear factor-kappa B (NF- kB) and NLRP3 inflammasome activation by P2X7/NLRP3/caspase 1 pathways are closely linked to Alzheimer's disease (AD) via neuroinflammation, therefore it could be a rational strategy to target these proteins to counteract the AD pathology. These strategies could work effectively if therapeutic intervention started at an early stage. This review highlights the potentials of drugs acting on the P2X7 receptor and its downstream protein targets for inhibition of neuroinflammation. Thus it might act as a futuristic strategy to treat Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a complex and diverse progressive neurodegenerative disorder of the CNS. It is caused by progressive memory loss, orientation, reasoning, functional abilities and severe cognitive decline (Fang et al., **2013**; Hardy and Selkoe, **2002**). The World Alzheimer Report (**2015**) estimates that 46.8 million people worldwide are suffering from dementia. These numbers will reach 74.7 and 131.5 million in 2030 and 2050 respectively. Prevalence of dementia is most commonly seen in the elderly population of Asia. Research showed that most people currently suffering from dementia have not received a proper diagnosis; whereas in India, 90% remain undiagnosed (Prince et al., **2016**). (Fig. 1) ("World Alzheimer Report 2015: The Global Impact of Dementia | Alzheimer's Disease International," **n.d.**)

A major pathological feature of the AD includes the excessive formation of neurofibrillary tangles (composed of hyperphosphorylated tau), senile plaques (consist of beta-amyloid, Aβ), and a deficiency in cholinergic neurotransmission. Extracellular aggregations of amyloid (Aβ) peptide caused loss of neurons in the hippocampus and cerebral cortex of the brain (Hardy and Selkoe, **2002**; Walsh and Selkoe, **2004**).

Revised guidelines recognize three stages of Alzheimer's diseas. One stage with dementia, two stages in which Mild cognitive impairment and Dementia are present and another stage is pre-clinical AD ("2018 Alzheimer's disease facts and figures," **2018**). According to the World Alzheimer report 2011, earlier diagnosis and early intervention are significant mechanisms to control AD. Hence targeting early stage is important to slow down the progression of the AD. (Table 1)

Abbreviations: NLRP3, NOD like receptor protein 3; ASC, apoptosis-related speck-like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; CARD, caspase recruitment domain; DAMPS, danger or damage associated molecular patterns; IL, interleukin; LRR, leucine-rich repeat; NACHT, central nucleotide-binding and oligomerization; NF-κB, nuclear factor kappa B; P2X7, P2X purinergic receptor 7; PAMPS, pathogen associated molecular patterns; PYD, pyrin domain; TLR, Toll-like receptor; MD2, Muramyl dipeptide

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Fig. 1. 10 warning signs of Dementia. (Alzheimer's report 2015).

2. Mild cognitive impairment (MCI)

It is a midway state of slide impairment in cognitive function, lies between normal aging and AD (Levey et al., 2006). However, it is unlike dementia in which cognitive deficits are more rigorous and have a significant effect on everyday functions (Gauthier et al., 2006). It referred to an early stage of the AD on the Global Deterioration Scale (Ganguli, 2014). Mild cognitive impairment is divided into two subtypes i.e. amnestic and nonamnestic. Amnestic MCI has high potential to develop into an AD (Petersen, 2004). MCI along with depression doubles the risk of the early AD in geriatrics (Modrego and Ferrández, 2004). MCI symptoms along with increased levels of beta-amyloid (MCI due to Alzheimer's disease) suggest that individual may be in the early stage of the AD. (According to revised guidelines for diagnosing AD published in 2011) Recently researcher identified a biomarker for MCI i.e. Neurogranin (Ng), a postsynaptic protein, have a significant association with memory and executive function only with individuals with MCI. Ng level elevated in the cerebrospinal fluid (CSF) of patients with AD and MCI compared to participants with normal cognition (NC). These findings suggest that CSF Ng has the potential to observe the progress of AD, acting as a biomarker for assessing the effect of treatment (Headley et al., 2018). (Fig. 2) (Krstic and Knuesel, 2013; Lovell and Markesbery, 2007).

3. Anti-amyloid clinical trials of drugs based on the Amyloid Hypothesis

Aβ is liberated from an amyloid precursor protein (APP) by the act of β-secretase and γ-secretase, which have been considered as therapeutic targets for the AD (O'Brien and Wong, 2011). So many anti-amyloid trials have failed in the clinical trials that caused many questions to the Amyloid Hypothesis itself. (Castello et al., 2014; Teich and Arancio, 2012). There is a list of Anti-amyloid clinical trials of drugs based on Amyloid Hypothesis (Aisen et al., 2011; Doody et al., 2013, 2014; Egan et al., 2018; Honig et al., 2018; Hopkins, 2011; Jama, 2011; Liang et al., 2011; Table 2). A current treatment for AD resolves symptoms and modestly improves disease condition but neither reverses or prevents disease (Rosenblum, 2014). Hence, there is a need to target other features of the neurodegeneration such as inflammation, the formation of advanced glycation end products (AGEs) and brain glucose metabolism (Münch et al., 1998; Venigalla et al., 2016).

4. Early event: microglia activation

Other pathological feature includes the gathering of activated microglia and astrocytes around amyloid (Aβ) plaques and damaged neurons (Selkoe, 2002). It has been found that accumulated Aβ in the plaque initiates an inflammatory process leading to stimulation of the neurodegenerative process (McGeer et al., 2000). Microglial cells, a type of glial cell, which increased inflammatory progression and tau phosphorylation, in the AD (Munoz and Ammit, 2010; Sastre et al., 2006). The activated microglial cell may cause neurodegeneration and decrease in cognitive impairment. In the chronic stage of neuroinflammation, activated microglia have the ability to induce further neuroinflammation in the brain. This condition may lead to blood-brain barrier (BBB) dysfunction. Failure of Aβ clearance may be due to BBB transporter dysfunction and a decrease in Aβ degrading enzyme. There may be BBB transporter dysfunction by upregulation of LRP-1(low-density lipoprotein receptor-related protein-1) and down-regulation of RAGE (receptor for advanced glycation endproducts) level. NEP (neprilysin), IDE (insulin degrading enzyme), ECE1(endothelin converting enzyme 1), ACE (angiotensin converting enzyme), and ECE2 plays important role in the degradation of Aβ. The overall impact of the above pathology may contribute due to the accumulation of Aβ. This accumulated Aβ may adversely affect synaptic function by down regulation of CREB (cAMP-response element-binding Protein) and a decrease in glucose uptake. Further, it may cause neurodegeneration and decrease in cognitive impairment, this pathophysiology may pave the way towards dementia and AD (Fig. 3) (An et al., 2018; Cai et al., 2014; Teich and Arancio, 2012) Hence it is necessary to shed light on other alternative clinical pathological features of the AD (e.g. activation of microglia). However, targeting microglia activation in the early stage is helpful later on it becomes detrimental in the neurodegenerative stage (Sarlus and Heneka, 2017).

5. Microglia

Microglial are monocyte-derived and popularly called the resident innate immune cells of the central nervous system (CNS) (Kettenmann et al., 2011). Microglia exist in two different types i.e. resident and the newly differentiated microglia (Soulet and Rivest, 2008). These cells respond quickly to harmful stimuli in the brain. Their main function is to protect brain neurons damage from pathogens like a virus, bacteria. They have the ability to eliminate cell debris as well as pathogens by performing phagocytosis process. Later on, they initiate tissue repair processes and wound healing to maintain brain health (Delpech et al., 2015; Dickson, 1999). They play a key role in surveying the local microenvironment and propagating inflammatory signals (Norden et al., 2015).

5.1. Microglial activation

Microglia in healthy mature CNS exists in a ramified form which consists of a small soma with the fine cellular process. This is the morphology occur in "resting state". Neurodegenerative diseases, infection, ischemia and altered homeostasis of the brain lead to drastic changes in morphology, gene expression, and functional behavior. This stage is called "Microglial activation". Microglial activation is multidimensional because activated microglial cells are able to produce detrimental as well as trophic effectors. Neuroprotection, as well as neurotoxicity, depends upon specific activating signals on microglial cells (Hanisch and Kettenmann, 2007). Microglial cells are dynamic in nature and showed region-specific responses upon activation by surrounding chemicals. They have the potential to readily alter phenotype upon changes in the surrounding. This specialty provides an explanation of region-specific CNS disorders (Lai et al., 2011).

Microglia have been a topic of interest due to its influence on Alzheimer's disease pathophysiology (Naert and Rivest, 2011).

Table 1
Three stages of Alzheimer's disease. (Source: Alzheimer's Association, 2018).

Stages	Features		
	Dementia due to Alzheimer's disease	MCI due to Alzheimer's disease	Preclinical Alzheimer's disease
Memory	Visible memory, thinking and behavioral symptoms		The absence of memory loss
Biomarkers	Confirmation of an Alzheimer's-related biomarkers changes	Confirmation of an Alzheimer's-related biomarker change	Have assessable changes to specify the earliest signs of disease Biomarkers from CSF, Blood
Cognition		Greater Cognitive decline than for their age and education level	
Everyday activities		Does not significantly impede with everyday activities	

Microglia activation has dual effects on AD progression that depends upon the duration of the activated stage. Initially, it caused a decrease in Aβ accumulation by stimulating phagocytosis, clearance, and degradation. On the other hand, chronic microglial activation leads to the secretion of pro-inflammatory cytokines, which contributes to neuronal loss (Jiang and Yu, 2012; Wang et al., 2015a, 2015b).

There is considerable evidence that supports inflammation in the brain due to normal aging. Brain aging leads to an increase in oxidative stress, lipid peroxidation and DNA damage (Wu et al., 2016). Microglia play a central role in CNS inflammation; on activation release various inflammatory mediators, interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which further induce a wide spectrum of inflammatory reactions. These reactions might further lead to neuronal injury due to an increase in the release of pro-inflammatory cytokines, ROS, cytotoxic substances and excitatory amino acids (Thompson and Tsirka, 2017). Microglial activation can be divided into acute or chronic depends upon the duration of the external signal and different factors such as stress, infection, inflammation, and signals from damaged neurons (Graeber and Streit, 2010). Microglial activation in chronic microglial activation stage paved the way towards degeneration of microglial cells. This condition may lead to secondary neurodegeneration (Liu et al., 2001; Polazzi and Contestabile, 2006).

It has been found that microglia can be activated into two subsets with dissimilar molecular phenotype i.e. classic (M1) or selectively activated state (M2 state) (Czeh et al., 2011). In the M1 state, activated microglial cells release proinflammatory cytokines, which caused damaging effect whereas in the M2 state secrete anti-inflammatory cytokines and neurotrophins, like IL-10, brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF), which are considered to be beneficial (McGeer and McGeer, 2015) Proinflammatory cytokinins released from M1 state plays the main role like defense against pathogens and tumor cells but, at the same time, it may lead loss of neurons. In contrast, the M2 state promotes tissue remodeling repair, important immunomodulatory and Angiogenesis (Soulet and Rivest, 2008; Wang et al., 2015a,b). Hence, it is rational to shift M1 to M2, acted as an effective therapy against AD (McGeer and McGeer, 2015) (Walker and Lue, 2015). However, some researcher suggested that macrophages or microglia do not exist in discrete polarized states, Instead, M2 phenotype appears to be enhanced by additional exposure to an inflammatory stimulus, signifying that inflammatory insult potentiates anti-inflammatory effect. That is expected to be involved during the immune response to the infection or injury (Smith et al., 2016).

5.2. *Microglial signaling*

There is a bidirectional communication between microglia and neurons, it is necessary for brain development and maintaining homeostasis. Microglial activity is controlled by neurons through the release of substances such as chemokines, neurotransmitters, and purinergic signaling. Microglia persuades neuronal function and connectivity by direct physical contact or release of paracrine signals (Simon et al., 2018).

In an experimental model, induction of the M1 state of microglia can be done by lipopolysaccharide (LPS) and interferon gamma (IFN-γ) in animals (Boche et al., 2013; Loane and Byrnes, 2010). IFN-γ acts on IFN-γ receptors and induced M1 activation via JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling

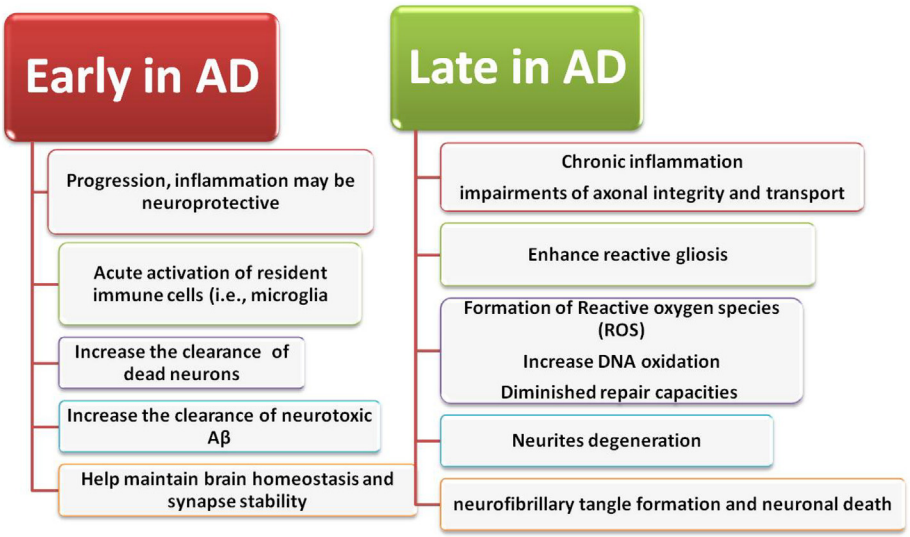

Fig. 2. Difference between features of the early and late AD.

Table 2
Anti-amyloid clinical trials of drugs based on the Amyloid Hypothesis.

Sr No.	Name of drug	Stage of disease	Method	Clinical trial phase	Reasons for failure		Ref
					Efficacy	Adverse events	
1	Verubecestat Target BACE-1 inhibitor	Mild-to-Moderate	A randomized, double-blind, placebo-controlled, 78-week trial	Phase III	Did not reduce the cognitive or functional decline in patients	Rash falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-color change	(Egan et al., 2018)
2	Solanezumab The humanized monoclonal antibody binds amyloid protein	Mild	A double-blind, placebo-controlled	Phase III	Did not significantly reduce the decline in cognition or function		(Honig et al., 2018)
3	Solanezumab The humanized monoclonal antibody binds amyloid protein	Mild-to-Moderate	A double-blind, placebo-controlled (EXPEDITION 1 and EXPEDITION 2),	Phase III	Failed to improve cognition or functional ability.	No adverse events	(Doody et al., 2014)
4	Semagacestat A small-molecule γ-secretase inhibitor	Mild-to-moderate	Randomized, double-blind, placebo-controlled trial	Phase III	Did not improve cognitive status significant worsening of functional ability	Skin cancers and infections	(Doody et al., 2013)
5	Tramiprosate Binds to soluble Aβ and reduces amyloid aggregation and subsequent deposition	Mild-to-moderate	A randomized, double-blind, placebo-controlled, multi-center study	Phase III	Did not show a significant treatment effect		(Aisen et al., 2011)
6	ELND006 l γ-secretase inhibitor	Healthy elderly subjects		Phase I Halted in the fall Oct 2010		Liver side effect	(Hopkins, 2011; Liang et al., 2011)
7	Tarenflurbil	Mild	A multicenter, randomized, double-blind, placebo-controlled trial	Phase 2 trial	Did not slow cognitive decline or the loss of activities of daily living in patients		(Jama, 2011)

pathway. This signaling cascade stimulates the release of M1-associated cytokines, chemokines (Boche et al., **2013**; Hu and Ivashkiv, **2009**). LPS binds to LBP (LPS-binding protein) to induced M1 activation. This complex interacts with Toll-like receptors 4 (TLR4) and co-receptors such as clusters of differentiation 14 (CD14), lymphocyte antigen 96 (MD2) stimulating a transmembrane signaling pathway. TLR4 signaling is divided into two different signaling pathways, the MyD88-dependent, and MyD88-independent pathways. In the MyD88-dependent pathways, there is activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) The activated NF-κB is then entered into the nucleus where it binds to sequences of DNA. This causes transcriptional up-regulation of M1-associated proinflammatory mediators (Takeda and Akira, **2004**; Venigalla et al., **2016**). In the MyD88 independent pathway, There is a phosphorylation of interferon regulatory factor 3 (IRF3). IRF3 enter into the nucleus and produce Interferon type 1 (IFN-β). Suppressor of cytokine signaling -1 (SOCS-1) downregulates this pathway. IFN-β further binds to the receptor and stimulates Janus family kinase, resulting in enrolment of signal transducers and activators of transcription (STAT1). There is a phosphorylation of STAT1. The phosphorylated form of STAT1 then enters into the nucleus and activates the unfavorable transcription of IFN stimulated gene (Venigalla et al., **2016**). Recently it has been demonstrated that alternative M1 activation stimulation could be done via granulocyte-macrophage colony stimulating factor (GM-CSF) (Lacey et al., **2012**). (Takeda and Akira, **2004**; Venigalla et al., **2016**)

M2 microglia activation produces a group of mediators such as anti-inflammatory cytokines, extracellular matrix proteins, glucocorticoids, and other substances (Subramaniam and Federoff, **2017**). M2 phenotypes of microglia are similar to the M2 phenotype of macrophages. In M2 phenotype, it produces mediators such as IL-4 and IL-10 (Chhor et al., **2013**; Freilich et al., **2013**). M2 phenotype activation is divided into M2a, M2b and M2c state (Boche et al., **2013**). The M2a state is related to tissue repair and phagocytosis, stimulated by IL-4 or IL-13 via the JAK/STAT pathway. The M2b state is associated with the recruitment of regulatory T cells by acting on TLRs and IL-1 receptor. This results in secretion of IL-10, CD86 (on the cell surface) and Major histocompatibility complex-II (MHC-II). M2c activation state is concerned with anti-inflammatory and curative functions, stimulated by IL-10 and glucocorticoid hormones (Franco and Fernández-Suárez, **2015**; Michell-Robinson et al., **2015**) Neurofibrillary tangles formation is another pathological hallmark of the AD. It mainly composed of hyperphosphorylated Tau protein. Inflammatory cytokines releases by microglia were able to mediate different kinases such as glycogen synthase kinase 3β, responsible for Tau phosphorylation. Hence Aβ induced activation of microglia and cytokine releases were able to induce hyperphosphorylated Tau protein (Kitazawa et al., **2004**; Li et al., **2003**)

5.3. Microglial receptors

Multiple signals unite on microglial cells to dynamically maintain or modify their functional state (Hanisch and Kettenmann, **2007**). There are several receptors present on the surface of the microglial cell includes Neurotransmitter Receptors, Receptors for Neurohormones and Neuromodulators, Cytokine and Chemokine Receptors, Pattern-Recognition Receptors (Kettenmann et al., **2011**).

5.3.1. Purinoceptors

Two families of the receptor for purines were identified, P1 receptor for adenosine and P2 receptor for ATP and adenosine 5′ diphosphate (ADP) (Burnstock and Kennedy, **1985**). P1 adenosine receptor is a G-protein coupled receptor, exists in the following four subtypes that are A_1, A_{2A}, A_{2B}, and A_3. These receptors are again classified according to the type of G-protein interaction i.e. Gi or Gs. A1 and A3 receptor interact with Gi. This interaction inhibits adenylate cyclase and decreased cyclic adenosine 5′-monophosphate level, whereas A_{2A} and A_{2B} receptor interact with Gs leads to activation of adenylate cyclase and

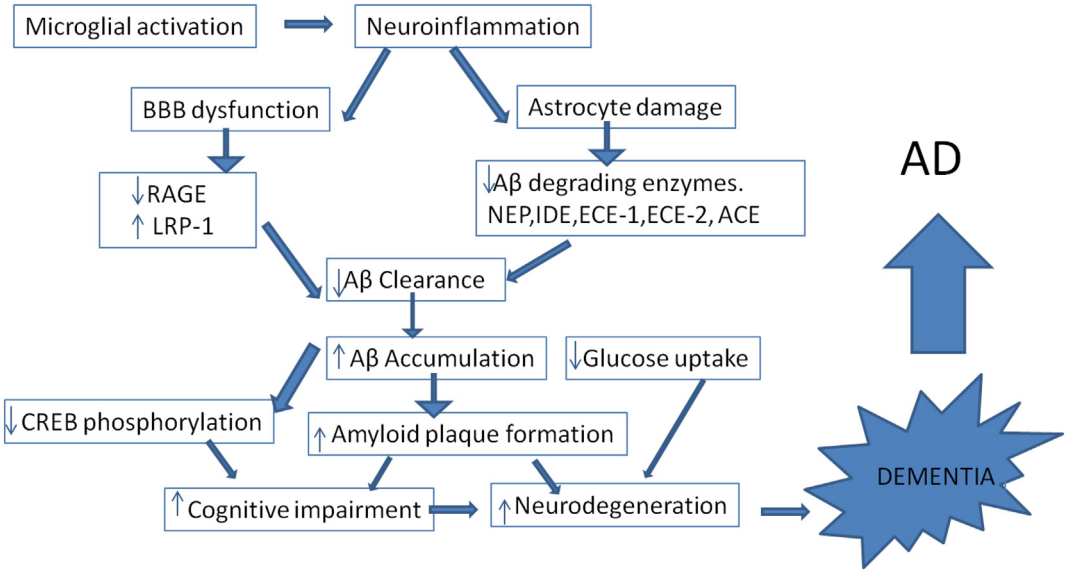

Fig. 3. Chronic microglial activation contributed to the pathogenesis of AD.

increase in production of cyclic adenosine 5′-monophosphate (Fredholm et al., 2001). (Gebicke-Haerter et al., 1996; Hammarberg et al., 2003; Heese et al., 1997; Lee et al., 2006; Saura et al., 2005; van der Putten et al., 2009) There are seven subtypes of P2X ion channel receptor and eight subtypes of P2Y, that are G-protein coupled receptor (Burnstock, 2007). Among the P2X receptor, (P2X7R) plays a vital role in neuroinflammation (Weisman et al., 2012).

5.3.1.1. P2X receptor

5.3.1.1.1. P2X7-NLRP3 pathway. The P2X7 receptor is a trimeric ATP-gated cation channel. Its activation results in a number of downstream events, including the release of proinflammatory mediators and cell death and proliferation.(Bartlett et al., 2014). The P2X7R is vastly expressed on immune cells, such as macrophages, mast cells, and microglial cells, and can also be found on oligodendrocytes but to a lesser extent in astrocyte and neurons. It is considered a “silent receptor,” in a normal state but overexpressed in pathological circumstances. Only high, millimolar ATP concentrations is responsible for the P2X7R activation, signifying that it has a high application under pathological condition (Jacobson and Müller, 2016; Wiley et al., 2011). The P2X7R has been associated to various chronic inflammatory neurological disorders like multiple sclerosis (MS), Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS) (Adinolfi et al., 2018). The P2X7 receptor was found overexpressed in the post-mortem brains of AD patients. Upregulated P2X7 receptor is also found in the microglia of the Aβ induced rats (Mclarnon et al., 2006). This condition may stimulate the activation of the non-amyloidogenic processing of APP (Amyloid Precursor Protein) (Darmellah et al., 2012). It is widely accepted that Aβ triggers the release of IL-1β via P2X7 receptor activation (Sanz et al., 2009). It has the ability to place in the membranes and form pore-like structures, which are permeable to Adenosine Triphosphate (ATP). Therefore Aβ increases extracellular ATP concentration causing activation of P2X receptors and potentiating excitatory synaptic activity (Sáez-Orellana et al., 2018; Sáez-Orellana et al., 2016). P2X7 receptor plays a new role in Aβ peptide-mediated release of chemokines CCL3, which is linked with pathogenic $CD8^+$ T cell recruitment in AD animal model. Also it has been found that P2X7R deficiency decreased Aβ load in APPPS1 mice (Martin et al., 2018). The P2X7/NLRP3 inflammasome pathway leads to the release of an IL-1 family of pro-inflammatory cytokines IL-1β, IL-18 and IL-33 (Bhattacharya and Jones, 2018; Di Virgilio, 2007; Latz et al., 2013). In this way, the P2X7 receptor involment was found to be most important for the generation of neuroinflammation in the brain via microglia activation by amyloid beta. Constant elevations in extracellular ATP and proinflammatory cytokines will support neuroinflammation and neurodegeneration (Takenouchi et al., 2010). Therefore, overactivation of P2X7 receptors on microglia by extracellular ATP may contribute neuroinflammation induced AD.

5.3.1.1.2. NLRP3 inflammasome. The NLRP3 inflammasome is the mainly studied inflammasome, has been correlated to diseases such as Alzheimer’s disease, atherosclerosis, metabolic syndrome, and age-related macular degeneration It is a multiprotein complex composed of NLRP3, ASC, and procaspase-1 (Ozaki et al., 2015). In the microglia, DAMP activates NFkB activation by phosphorylation of the Toll-like receptor. This signal is considered as a priming event. Then,the activated NFkB in the nucleus promote transcription of proinflammatory cytokines pro-IL-1β, pro-IL-18 and NLRP 3. A subsequent stimulus (signal 2) activates the NLRP3 inflammasome by facilitating the oligomerization of inactive NLRP3, apoptosis-associated speck-like protein (ASC), and procaspase-1 (Shao et al., 2015) The LRR domain of NLRP3 is possible to be involved in sensing the danger signal. NACHT domains responsible for oligomerization of NLRP3 monomers and, The PYD effector domain of NLRP3 has an ability to interacts with the PYD domain of ASC (Doyle et al., 2015; Ozaki et al., 2015). ASC act as an adaptor protein, recruiting procaspase-1 via its CARD domain. Procaspase-1 produce the two fragments (i.e., p20 and p10) which are a tetrameric form of the active caspase-1. Active cleaves the precursor proinflammatory cytokines pro-IL-1β and pro-IL-18 into their mature secreted forms (Lamkanfi, 2011) IL-1β is a chief proinflammatory cytokine that plays a noteworthy role in the pathogenesis of neurodegenerative diseases like an AD. IL-1β level found elevated in AD patient (Allan et al., 2005) P2X7R activation also releases TNF-α, IL-18, and IL-6 (Shieh et al., 2014). Chronic alcohol exposure was able to induce neurodegenerative brain damage by acting on P2X7R and P2X4R. Ethanol in 25 and 100mM was found to increase the release of IL-1β via activation of P2X7 from murine BV2 microglia cells (Asatryan et al., 2018). Aβ has been found to increase the release of ATP and indirectly involved in the excessive release of IL-1β level in microglia from wild-type but not from P2X(7)-deleted mice (Sanz et al., 2009). Hence, antagonizing P2X7R is the best approach to control neuroinflammation in the AD patients (Heppner et al., 2015) (Fig. 4) (Di Virgilio, 2007; Latz et al., 2013; Shieh et al., 2014; Weisman et al., 2012).

Subtype P2X4 receptor contributes to neurodegeneration in the AD.

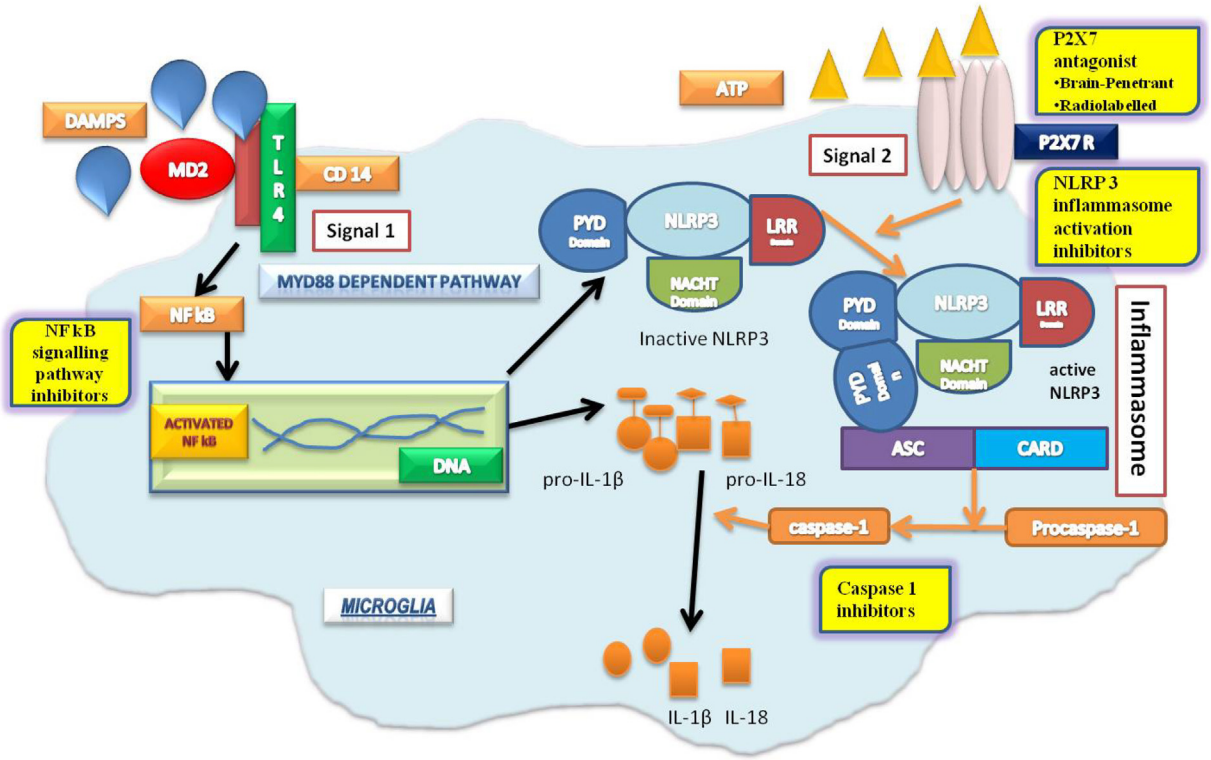

Fig. 4. Therapeutic Targets of P2X7-NLRP3 pathway in AD.

It has been suggested that overstimulation of the P2X4 receptor due to an increased level of ATP from microglia leads to neuronal cell death. This excessive release of ATP is due to an increased level of Aβ in AD patient (Varma et al., 2009).

5.3.1.2. P2Y receptor. P2Y1 receptor plays a vital role in the process of neurogenesis due to the proliferation of neural stem cells (NSC) by endogenous agonist ADP in the mammalian hippocampus (Mu and Gage, 2011; van Praag et al., 2002). UTP induced uptake as well as degradation of Aβ1-42 by binding to the P2Y2 receptor (Kim et al., 2012). It stimulates neurite extension and non-amyloidogenic APP processing due to an increased level of IL-1β. P2Y2 activation is most important in regulating neuroprotective response during neuroinflammation (Peterson et al., 2013; Woods et al., 2016). Like P2Y2, P2Y4 receptor plays an important role by increasing uptake of Aβ1-42 by rat microglial cell via ATP signaling (Li et al., 2013). UDP act on the microglial P2Y6 receptor to regulate phagocytosis of damaged neurons. However, targeting this receptor in AD treatment may be complicated due to phagocytosis of the healthy neuron by activated microglia. This process is called phagoptosis (Brown and Neher, 2014). Microglia P2Y12 receptors stimulate neuroprotective responses, by inducing microglial immigration in the direction of injurious stimuli and defending neurons from ROS-induced neurotoxicity (Haynes et al., 2006).

6. Modulation of microglial activation by drugs

6.1. PPAR γ Agonist

Pioglitazone treatment showed the shifting of M1 state, into the M2 state by PPARγ activation in a Murine Model of Alzheimer's Disease. The mechanism behind shifting was related to increased phagocytosis of deposited forms of amyloid. This mechanism contributes to the therapeutic use of PPAR γ agonists for the treatment of Alzheimer's disease (Agarwal et al., 2017; Mandrekar-Colucci et al., 2012). IL-12 and IL-23 cytokines control the differentiation of Th1 and Th17 cells, which may limit the efficacy of Aβ immunotherapy for the treatment of AD. 15d-PGJ2 (15-Deoxy-Δ12, 14-ProstaglandinJ2) (PPAR-γ agonist) was found to inhibit production of IL-12 and IL-23 in Aβ plus LPS-activated microglia. It also inhibits the production of an IL-1β cytokine. It suppresses inflammation by inhibiting the expression of MyD88-dependent signaling intermediates. Hence, could be useful for the treatment of AD (Xu et al., 2008).

6.2. NF-κB signaling pathway inhibitors

Tanshinone I inhibit synthesis and/or expressions of several pro-inflammatory M1 mediators such as nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 also distinctly inhibit NF-κB activation in LPS-induced microglia (Fu et al., 2018; Wang et al., 2015a, 2015b). The phenolic glucoside gastrodin, obtained from the *Gastrodia rhizoma* considerably decrease levels of neurotoxin proinflammatory mediators and cytokines by inhibition of the NF-κB signaling pathway and phosphorylation of MAPKs in LPS-stimulated cultured murine microglial BV-2 cells. It suppresses microglial activation hence attenuates neuroinflammation (Dai et al., 2011; Li et al., 2018a, 2018b). Resveratrol inhibits pro-inflammatory enzymes and cytokines by means of down-regulating phosphorylation of NF-κB, CREB and MAPKs family in a mTOR-dependent manner in lipopolysaccharide (LPS)-stimulated murine microglial BV-2 cells. Also, it has been found to inhibit microglial activation by a SIRT1-SOCS1 pathway in the LPS/IFN??-treated N9 microglia (Zhang et al., 2017; Zhong et al., 2012). Trans-cinnamaldehyde (TCA) is a active constituent isolated from the stem bark of *Cinnamomum cassia*, was able to improve memory impairment and synaptic damage by inhibiting microglial activation in LPS induced mice. It accelerates degradation of iNOS mRNA that leads to inhibition of MEK1/2-ERK1/2 signaling pathway result in a decrease in production of NO (Zhang et al., 2016) Glatiramer Acetate (GA) promotes the phagocytic activity by stimulating the secretion of IL-10 while it decreases the release of TNFα. in primary rat microglia cells. At

Table 3
NF-κB signaling pathway inhibitors.

Sr. No	Tool compounds	Description	Ref
1	Tanshinone-I	Decrease the formation of M1-pro-inflammatory mediators (nitric oxide, TNF-a, IL-6, and IL-1b). It inhibits NF-kB expression	(Wang et al., 2015a, 2015b; Fu et al., 2018)
2	PPAR agonists	It causes shifting of microglia from M1 state to the M2 state	(Mandrekar-Colucci et al., 2012; Xu et al., 2008)
	Pioglitazone and Rosiglitazone 15d-PGJ2	It suppresses inflammation by inhibiting the expression of MyD88-dependent signaling intermediates	
3	Glatiramer acetate	Stimulating the secretion of IL-10 while it decreases the release of TNFα	(Pul et al., 2011)
4	Gastrodin	Decrease levels of neurotoxin proinflammatory mediators and proinflammatory cytokines	(Dai et al., 2011; Li et al., 2018a, 2018b)
5	Resveratrol	Inhibit proinflammatory enzymes and proinflammatory cytokines	(Zhong et al., 2012; Zhang et al., 2017)
6	Trans-cinnamaldehyde (TCA)	Improve memory impairment and synaptic damage by inhibiting microglial activation The decrease in NO production	(Zhang et al., 2016)
7	Rhinacanthin C	Inhibited IL-6 and TNF-α secretion induced by LPS-, Aβ-, and IFN-γ- in Microglia via NF-κB and ERK activation inhibition in Microglia	(Chuang et al., 2017)

the same time, it does not have any effect in the NO(Nitric oxide) production ((Pul et al., **2011**). R hinacanthin C (RC), a naphthoquinone ester obtained from *Acanthus nasutus Kurz* (Acanthaceae) suppressed overproduction of inflammatory cytokines via inhibition of NF-κB and ERK activation induced by LPS,I FN- γ and Aβ in BV2 microglia. This anti-inflammatory effect of RC in microglia could be a useful novel therapeutic agent in the AD (Chuang et al., **2017**) *Bacopa monnieri* (L) Wettst (common name, bacopa) is considered to be a "medhya rasayana" (an herb that sharpens the intellect and the mental power), in Aurveda significantly inhibited the release of proinflammatory cytokines IL-6 and TNF-α in LPS-activated N9 microglial cells *in vitro* (Nemetchek et al., **2017**) (Table 3).

6.3. Novel target: purinergic receptors on Microglia

Purinergic receptors could be a novel target in the treatment of AD. P2X7R subtype was found to be a dominant receptor in controlling neurodegenerative disorders. The evidence came from *in-vitro* studies and animal data about the role of P2X7R in the AD. The P2X7R antagonist should undergo a clinical trial to become the rational target to control AD (Burnstock, **2016**; Woods et al., **2016**) In the early stage of disease, targeting P2Y2R may have therapeutic value due to its role in tissue repairing. Activation of P2Y6R is complicated due to its dual role i.e. phagocytosis and phagoptosis hence required further studies to understand its role. Purinergic receptors on the microglial cell, due to its role in neuroprotective as well as neurodegeneration, represent a novel therapeutic target in the AD (Woods et al., **2016**).

6.3.1. P2X7R antagonist

The P2X7R antagonist has potential in the treatment of chronic pain, neuroinflammation, cancer but did not show for rheumatoid arthritis (Park and Kim, **2017**). It is involved in the inhibition of neuroinflammation, could be beneficial in the treatment of many neurodegenerative diseases in which inflammation is a basis of neuronal death such as Alzheimer's disease. There has been development of current interest in the pathophysiological roles of P2X7R and the prospective of P2X7R antagonists to treat neurodegenerative diseases, mood disorders, amyotrophic Lateral sclerosis, multiple sclerosis and epilepsy (Bhattacharya, **2018**; Burnstock and Knight, **2018**; Chrovian et al., **2014**; De Marchi et al., **2016**). An abnormally up-regulated inflammatory response by glial activation may aggravate neurodegeneration. Based on the fact of epidemiology studies, on long-term users of non-steroidal anti-inflammatory drugs, i.e. ibuprofen and indomethacin, have considerably lesser frequencies of neurodegenerative disease, including Alzheimer's disease (AD) and Parkinson's disease (Takenouchi et al., **2010**). P2X7R-mediated common disease pathways in central nervous system (CNS) disorders of unlike etiology. P2X7R is an ideal drug target because antagonism takes place only if the channel is activated in high ATP concentration, which is believed to be increased during pathology of neuroinflammatory disorders. Hence antagonism would not cause any adverse effect (Bhattacharya, **2018**; Burnstock and Knight, **2018**; Sperlágh and Illes, **2014**). P2X7R antagonists might be an effective treatment for neuroinflammation induced-neurodegenerative diseases like Alzheimer's disease (Sáez-Orellana et al., **2016**; Woods et al., **2016**). Various preliminary studies suggested the role of P2X7R antagonists in the AD. Reactive microglia and β-amyloid peptide (Aβ) plaques are hallmarks of the AD. In one of the studies using wild-type and P2X7R deficient mice, Aβ caused ATP release, IL-1β secretion, and plasma membrane permeability in wild-type mice but did not produce in P2X7R deficient mice (Sanz et al., **2009**). Hence, Aβ has an ability to produce neuroinflammation via modulation of P2X7R. Brilliant blue G (BBG) is P2X7R antagonist which is obtained from a blue food dye called FD&C blue No. 1. It is able to cross the blood-brain barrier, and safe in healthy animals (Borzelleca et al., **1991**). BBG remains one of the most widely used and useful antagonists as it act on human, mouse, rat, dog and guinea pig P2X7R (Young and Górecki, **2018**). It has been found to improved cognition and the development of dendritic spines in Aβ-42-injected rats (Chen et al., **2014**). It is neuroprotective and antagonized inflammatory responses induced by the P2X7R agonist in Aβ- peptide-injected rat brain (Ryu and McLarnon, **2008**). Many drugs have been tried to target central nervous system P2X7 receptor but unfortunately, only a few compounds possessed property to cross the BBB (Blood-Brain Barrier) (Hopper et al., **2012**). Pfizer Company developed CE-224535 for targeting the P2X7 receptor. It failed to show usefulness in Rheumatoid arthritis. However, improved pharmacokinetic properties as well as proven tolerance in clinical trials, make it an excellent candidate for the study of neurodegenerative diseases (Duplantier et al., **2011**). GlaxoSmithKline has developed P2X7 receptor antagonist (GSK1482160). It has reported better CNS penetration and also has the ability to be radiolabelled with ^{11}C. Radiolabelled ^{11}C-GSK1482160 showed strong P2X7 selectivity and act as a biomarker of neuroinflammation in LPS challenged rats (Gao et al., **2015**; Territo et al., **2017**)

6.3.1.1. Brain-Penetrant P2X7R antagonist. The amide GSK1370319A also showed good brain penetration. It prevents neurodegeneration and the formation of the inflammasome induced cell death (Baudelet et al., **2015**; Murphy et al., **2012**). Janssen laboratories developed two new brain-penetrant P2X7 antagonists, JNJ-54175446 and JNJ-55308942 (Chrovian et al., **2018a**; Letavic et al., **2017a**). Both molecules retain selectivity in rodents that made the opportunity to perform preclinical studies in a rodent model of disease (Bhattacharya, **2018**). The promising role of the P2X7 receptor in neuroinflammation and related diseases has led to a shift in efforts toward the advancement of brain-penetrant antagonists (Rech et al., **2016**). Positive results in Clinical trials of CNS P2X7 antagonists could provide hope towards the development of drugs for Alzheimer's disease. Table 4

Table 4
Brain penetrant P2X7 antagonist.

Sr. No	Tool compounds	Indication	Specificity	Ref
1	A-438079	neonatal seizures	Rat	(Rodriguez-Alvarez et al., 2017)
2	Polycyclic carboranes	Antidepressant	Rat	(Wilkinson et al., 2014)
3	Phenyl-Substituted 5,6-Dihydro-[1,2,4]triazolo[4,3-a]pyrazine	Mood disorder	Rat	(Chrovian et al., 2016)
4	5,6-(Dihydropyrido[3,4-d]pyrimidin-7(8H)-yl)-methanones	neuropsychiatric disorders	Rat and Human	(Ziff et al., 2016)
5	4-(R)-methyl-6,7-dihydro-4H-triazolo[4,5-c]pyridines	CNS	Rat and Human	(Letavic et al., 2017a,b)
6	6-Methyl-4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridines	Mood disorder	Rat	(Chrovian et al., 2018a,b)
7	6,7-dihydro-[1,2,4]triazolo [4,3-a]pyrazin-8(5H)-	CNS	Rat and Human	(Ameriks et al., 2016)
8	N-((4-(4-phenyl-piperazin-1-yl)tetrahydro-2H-pyran-4-yl)- methyl)-2-(phenyl-thio) nicotinamide	Mood disorder	Rat, mouse and Human	(Letavic et al., 2013)
9	2-methyl-N-((1- (4-phenylpiperazin-1-yl)cyclohexyl)methyl)-1,2,3,4-tetrahydroisoquinoline-5-carbox-amide	Mood disorder	Rat, mouse and Human	(Letavic et al., 2013)
10	1,2,3-triazolopiperidines	Mood disorder	Moderate in rodents and Potent in Human	(Savall et al., 2015)
11	A804598	Chronic alcohol and high fat diet induced neuroinflammation in C57BL/6J Mice	Mice	(Freire et al., 2018)

6.3.1.2. P2X7 receptor-selective radiotracer. Development of radiotracer is essential for the diagnosis and monitoring of CNS disorder. In the last decade, various PET tracers have been developed and evaluated. A radiolabelled carbon-11 PET tracer [(11)C]A-740003 showed limited brain uptake but act as a better radiotracer for locating neuroinflammation by positron emission tomography in different rodent AD models (Janssen et al., **2014**). [11C]SMW139 binds especially to P2X7R in vivo in a rat model overexpressing the human P2X7 receptor and act as a promising PET the tracer of neuroinflammation in microglial activation (Janssen et al., **2018**). A novel a fluorine-18 PET tracer is superior and has a longer half-life. A novel P2X7 tracer [18F]EFB 2-cyano-1-(4-[18F]fluorobenzyl)-3-(quinolin-5-yl) guanidine developed with A-804598, showed strong affinity to human and rodent P2X7 and partial BBB penetration in the *in vitro* studies (Fantoni et al., 2017). A radiolabelled carbon-11 PET tracer has been successively used for molecular target (P2X7 receptor) on microglia for PET Imaging of Neuroinflammation. Following are the examples of radiolabelled carbon-11 PET tracer [^{11}C]A-740003, [^{11}C] SMW139, [^{11}C]JNJ-54173717, [^{11}C]GSK1482160 (Narayanaswami et al., **2018**; Table 6)

6.3.2. NLRP3 activation inhibitors

Pterostilbene (10 μM) attenuated Aβ1 − 42 activated NLRP3/caspase-1 inflammasome pathway in BV-2 microglia (Li et al., **2018a**,**b**). A small molecule NLRP3 inflammasome inhibitor (JC-124) inhibits the caspase-1 cleavage and activation in the TgCRND8 mice. JC-124 (50 mg/kg/day) by intraperitoneal injection five times per week for 4 consecutive weeks treatment led to decreased levels of Aβ deposition and decreased levels of soluble and insoluble $A\beta_{1-42}$ in the brain of TgCRND8 mice (Yin et al., **2018**). MCC950 (10 mg/kg in PBS) every second day for 3 months prohibited inflammasome activation and IL-1β release from microglia. Moreover, it promoted Aβ phagocytosis in the APP/PS1 mouse model of the AD (Dempsey et al., **2017**). APP/PS1 mouse model represents a novel AD model since it did not have NLRP3 protein. Edaravone inhibited NLRP3 inflammasome in Aβ-treated microglia, obtained through primary microglia cultures which were isolated from C57BL/6J mice. Benzyl isothiocyanate (BITC) is a naturally occurring compound originate in cruciferous vegetables, BITC (1, 5 and 10 μM) inhibited the secretion of IL-1β, inflammasome activation (NLRP3) and proinflammatory mediators, such as mitochondrial reactive oxygen species (ROS) and adenosine triphosphate (ATP) secretion induced by *E. coli* LPS in the BV2 microglial cells (Lee et al., **2016**). Fenamate class of NSAIDs was found to be a potent, reversible and selective inhibitor of the NLRP3 inflammasome. It acts via reversible blockade of Cl^- channel VRAC volume-regulated anion channels (VRAC), which played a vital role in regulating the NLRP3 inflammasome in the Aβ-induced memory deficit and Transgenic mouse (3xTgAD) model of Alzheimer's disease. Osmotic minipump at 25 mg/kg/ day for 28 days completely decreased memory deficits in the 3xTgAD mice. Therefore, it may offer clinical benefit in the AD (Daniels et al., **2016**). Stavudine (Nucleoside reverse transcriptase inhibitor) at a 50μM concentration down regulate NLRP3 inflammasome activation and Aβ autophagy in cell cultures of THP-1-derived macrophages induced by Aβ (La Rosa et al., **2018**). Artemisinin is obtained from *Artemisia annua*, is well known for its antimalarial effect. It has been found effective in an AD by inhibition of activation of NF-κB and NLRP3 inflammasome in 5-month-old APPswe/PS1dE9 transgenic mice. The treatment was given daily with 40 mg/kg artemisinin for 30 days by intraperitoneal injection (Shi et al., **2013**). Dihydromyricetin (DHM) at 1 mg/kg DHM intraperitoneally treated in APP/PS1 double-transgenic mice for 4 weeks. Transgenic mice showed decreased activation of NLRP3 inflammasomes and decreased expression of NLRP3 inflammasome components. Further, It reduced memory and cognition deficits in the AD (Feng et al., **2018**; Table 5).

Table 5
Drugs targeting NLRP3/Caspase 1 pathway.

Sr no.	Name of the tool compound	Animal screening model	Pathway affected	Ref
1	Pterostilbene (10 μM)	Aβ1 – 42 activated BV-2 microglia	NLRP3/caspase-1 inflammasome	(Li et al., 2018a,b)
2	JC-124 (50 mg/kg/day)	TgCRND8 mice	NLRP3 inflammasome inhibitor	(Yin et al., 2018)
3	Edaravone	Aβ-treated microglia (isolated from C57BL/6J mice	Inhibited NLRP3 inflammasome	(Wang et al., 2017)
4	MCC950 (10 mg/kg in PBS)	APP/PS1 mouse	Prohibited inflammasome activation	(Dempsey et al., 2017)
5	Stavudine (50 μM)	THP-1-derived macrophages induced by Aβ	NLRP3 inflammasome activation	(La Rosa et al., 2018)
6	Benzyl isothiocyanate	*E. coli* LPS in the BV2 microglial cells	inflammasome activation (NLRP3)	(Lee et al., 2016)
7				
8	Artemisinin (40 mg/kg)	5-month-old APPswe/PS1dE9 transgenic mice	inhibition of activation of NF-κB and NLRP3 inflammasome	(Shi et al., 2013)
9	Fenamate	3xTgAD mice	NLRP3 inflammasome	(Daniels et al., 2016)
10	Dihydromyricetin (DHM) at 1 mg/kg	APP/PS1 double-transgenic mice	Activation of NLRP3 inflammasomes	(Feng et al., 2018)
11	Bacopa (tea infusion 12.5–50 μg/ml)	LPS-activated N9 microglial cells	caspase 1, caspase 3	(Nemetchek et al., 2017)
	VX-765 (at 50 mg/kg)	J20 and Caspase-1 null J20 mice	caspase 1	(Flores et al., 2018)

Table 6
PET **i**maging of **n**euroinflammation: **p**otential **r**adiotracers.

Sr. no	Tracer of neuroinflammation	Radiotracer investigated	Different screening models	Ref
1	A-740003	[^{11}C]	Healthy rat	(Janssen et al., 2014)
2	SMW139	[^{11}C]	Autoradiography in a rat model	(Janssen et al., 2018)
3	GSK1482160	[^{11}C]	Rodent model multiple sclerosis	(Gao et al., 2015; Han et al., 2017)
4	JNJ-54173717	[^{11}C]	Rats and Non-human primates	(Ory et al., 2016)
5	TZ6019	[^{123}I]	Mouse model of Alzheimer disease	(Jin et al., 2018)
6	A804598	[^{3}H]	THP-1 cells	(Donnelly-Roberts et al., 2009)
7	JNJ-54232334	[^{3}H]	Wild-type and P2X7 knockout mice	(Lord et al., 2015)
8	A-740003	[^{3}H]	Autoimmune encephalomyelitis in Lewis rats (multiple sclerosis)	(Beaino et al., 2017)
9	IUR-1601	[^{18}F]	A radioligand competitive binding assay	(Gao et al., 2018)
10	EFB	[^{18}F]	Calcium influx assays using HEK293 and in B16 cells LPS induced neuroinflammation in rats	(Fantoni et al., 2017)
11	JNJ-64413739	[^{18}F]	Healthy humans	(Bhattacharya, 2018)

6.3.3. Caspase inhibitors

Casp1 represents a realistic therapeutic target against age reliant cognitive impairment and AD. Bacopa inhibited the activity of enzymes Matrix Metalloproteinase-3 (MMP-3), caspase 1, caspase 3 that play a vital role in neuroinflammation and neurodegeneration in the cell-free assay (Nemetchek et al., **2017**). VX-765 (at 50 mg/kg) dose-dependently prevents progressive amyloid-beta peptide accumulation, reverses brain inflammation, and maintain normal synaptophysin protein levels in (J20) the mouse hippocampus by inhibiting Caspase 1 enzyme. Similar protective features were obtained in Caspase-1 null J20 mice, therefore VX-765 was found to be a selective caspase 1 inhibitor in the treatment of AD (Flores et al., **2018**; Table 5).

7. Conclusion

Nuclear factor-kappa B (NF-κB) and NLRP3 inflammasome activation play a crucial role in the development of neuroinflammation, which is closely linked to the AD. Suppressing NALP3 inflammasome activation and NF-κB activity may provide clinical benefit in AD pathology. This review provides an inclusive overview of the modulation of microglia activation by shifting of M1 to M2 phenotype as well as targeting microglia receptor (e.g. purinoreceptor) using different drugs. These targets are extensively examined by various *in-vitro* studies. Various herbs found to inhibit release of proinflammatory mediators, shifting to the anti-inflammatory M2 phenotype of microglia and inhibition of Nuclear factor-kappa B activation. In this way, these herbs were found to be neuroprotective in nature during neuroinflammation in the early onset of disease. The P2X7R activation is responsible for the development of neuroinflammation via an NLRP3/caspase-1 pathway. Activation of NLRP3 inflammasome is a critical factor to initiate the process of neurodegeneration, Hence P2X7 antagonist, inhibitor NLRP3 inflammasome activation and caspase-1 are the promising targets in the neuroinflammation induced AD. P2X7 antagonist specific for the central nervous system has been explored for different psychiatric disorders. Therefore, it would be a rational strategy to study for Alzheimer's disease due to its expression on microglia. Recent reports on radiolabelled ligands of the receptor to visualized neuroinflammation using positron emission tomography would provide help to diagnose in the early stage of the disease. Thus the present review strongly supports the use of purinoreceptor i.e. P2X7 on microglia and downstream proteins such as Nuclear factor-kappa B, caspase 1 and NLRP3 inflammasome are an important target to treat an neuroinflammation induced the AD.

Conflict of interest

None declared.

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