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# Pharmacological Advances in Targeting Neuroinflammation for Alzheimer's Disease

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ABSTRACT

**Background:** Alzheimers disease AD is a progressive neurodegenerative disorder characterized by synaptic dysfunction neuronal loss and cognitive decline. Increasing evidence identifies chronic neuroinflammation as a central pathogenic mechanism in AD driven by amyloid beta accumulation.

**Purpose:** The purpose of this review is to critically examine recent pharmacological advances targeting neuroinflammatory mechanisms in AD with emphasis on molecular signaling pathways glial activation dynamics and emerging disease modifying therapeutic strategies.

**Methods:** A comprehensive literature survey was conducted using PubMed Web of Science and Google Scholar to identify relevant preclinical and clinical studies focusing on neuroinflammation targeted interventions in AD. Evidence related to cytokine and eicosanoid signaling inflammasome activation microglial immunoreceptors nonsteroidal anti inflammatory drugs biologics and nanotechnology based drug delivery systems was systematically analyzed.

**Results:** Mechanistic studies demonstrate that pharmacological modulation of microglial phenotypes inhibition of pro inflammatory mediators TNF alpha IL 1 IL 6 and targeting pathways such as NF kappa B NLRP3 inflammasome p38 MAPK JAK STAT and TREM2 can attenuate neuroinflammatory cascades and reduce amyloid beta and tau associated neurotoxicity. However clinical translation remains inconsistent due to limited blood brain barrier permeability off target toxicity and patient heterogeneity. Advanced nanocarrier based delivery systems and intranasal strategies show promise in improving brain bioavailability and therapeutic precision.

**Conclusion:** Targeting neuroinflammation represents a mechanistically robust avenue for disease modification in AD. Future therapeutic success will likely depend on integrated multimodal strategies combining precise inflammatory pathway modulation with advanced brain targeted drug delivery and biomarker guided patient stratification.

## 1. Introduction

Innate immune system activation in the brain is known as neuroinflammation and its main purpose is to defend the central nervous system CNS from illness injury and viral assaults. It is well known that neurological conditions like AD are actively influenced by neuroinflammation (F. Zhang & Jiang, 2015). Although the pathophysiology and etiology of the disease are constantly being improved upon diagnostic capabilities and the development of pharmaceutical therapies that might prevent or stop the disease are still limited. AD is currently incurable. Despite extensive preclinical and clinical research the drugs now in use only slightly alleviate symptoms in a small percentage of patients and do not address the fundamental causes of the illness (Bronzuoli *et al.*, 2016). This failure is most likely caused by our limited understanding of the molecular and cellular mechanisms involved in the pathophysiology of AD as well as approved treatments that have a coarse effect on both glutamatergic and cholinergic neurotransmission. On the other hand a large number of recently developed drugs are focused on changing the disease process itself by influencing one or more of the numerous extensive brain alterations brought on by AD. These alterations offer possible targets for new drugs that aim to halt or reduce the progression of the disease (Querfurth & LaFerla, 2010).

The multifactorial nature of AD is now widely acknowledged. Widespread oxidative stress glutamate excitotoxicity mitochondrial damage neuroinflammation the development of neurofibrillary tangles NFTs and beta amyloid Aβ deposition that results in senile plaques are its pathological hallmarks (Jurcău *et al.*, 2022). Pro inflammatory cytokine signalling has a variety of consequences in both neuroprotection and neurodegeneration. Immune

mediators are released when pro inflammatory signalling is triggered which impairs neuronal function and results in cell death. Neuroinflammation is also a result of a weak anti inflammatory system. Many pathways including NFκB Akt mTOR p38 MAPK caspase nitric oxide and COX influence the pathophysiology of AD by inducing brain immune cells such as microglia and astrocytes to release inflammatory cytokines including chemokines interleukins and tumor necrosis factor (Thakur *et al.*, 2023).

Cholinesterase inhibitors can be used for individuals with AD at any stage and memantine can be used for those with mild to severe dementia. The primary drugs that have been authorized are donepezil galantamine memantine and rivastigmine. But only when prescribed at the right time may drugs enhance the standards of life (Scheltens *et al.*, 2018). In 2021 aducanumab the first monoclonal antibody anti Aβ and the most recent AD drug was granted authorization by the US Food and Drug Administration FDA twenty years after memantine. Besides the whole thrill this new drug is costly and its advantages are not quite clear (Mafi *et al.*, 2022). In regard to this the current study set out to summarize the most important developments in the pharmacological treatment of AD by reviewing the most recent clinical trial data recorded by the US National Institutes of Health with the hope of providing theoretical background for drug discovery pipelines and future clinical practice.

## 2. Pharmacological Basis of Neuroinflammation in AD

According to Sierksma *et al.* (2020) AD is a prevalent neurodegenerative illness that is typified by widespread synaptic and neuronal loss memory loss and a marked cognitive decline. The neuropathological features prevalent in AD patients include extracellular amyloid plaques formed from Aβ and intracellular NFTs composed of hyperphosphorylated tau protein (Alzheimer's Association, 2019). The amyloidogenic process of amyloid precursor protein cleavage which is mediated by beta secretase and gamma secretase is necessary for the synthesis of neurotoxic Aβ (Si *et al.*, 2023).

The quad partite structure of synapses is made up of an astrocytic process a dendritic spine which is directly connected to a microglial cell and an axon terminal (Schafer *et al.*, 2013). The brain resident macrophages microglia and astrocytes are vital for the development of neuronal circuits and the homeodynamics of synapses in adulthood. Supporting synaptogenesis the sprouting of dendritic and axonal spines and controlling synaptic resilience depend on astrocytes (Arranz & De Strooper, 2019; Cohen & Torres, 2019; Stojiljkovic *et al.*, 2019).

Genome wide association studies GWAS revealed more than 40 susceptibility gene variations linked with an increased risk of acquiring late onset AD (Kamboh, 2018). These findings include immune response related genes namely CD33 ABCA7 CLU EPHA1 CR1 MS4A and HLA DRB5 HLA DRB1. The significance of neuroinflammation is currently supported by large scale GWAS which demonstrate that people with unusual microglial immunoreceptor variations TREM2 which encodes the triggering receptor expressed on myeloid cells 2 protein expressed on cells of the myeloid lineage have a significantly higher possibility of suffering from late onset AD (Bradshaw *et al.*, 2013; Griciuc *et al.*, 2013; Guerreiro *et al.*, 2013; Rathore *et al.*, 2018).

It is also commonly acknowledged that the inflammation characteristic of AD is strongly linked to oxidative stress (Rojas Gutierrez *et al.*, 2017). The causes of increased ROS production in the AD brain have been explored in the majority of studies addressing oxidative damage in AD. Transition metal catalyzed ROS generation may generally play a significant role particularly when the metal is liganded with Aβ. Additionally AD is characterized by malfunctioning mitochondria which can lead to increased ROS production (Ganguly *et al.*, 2021). AD encodes aspects that influence the glial removal of misfolded proteins and the inflammatory response. Systemic inflammation and obesity are examples of external variables that may disrupt immune functions in the brain and hasten disease progression (Heneka *et al.*, 2015).

Overall inflammatory mediators such as cytokines chemokines ROS and TNF alpha are released as a result of the interaction between oxidative stress neuroinflammation tau hypophosphorylation and beta amyloid buildup. These mechanisms induce astrocytes and microglia which leads to persistent neuroinflammation. The increasing neurodegeneration and cognitive impairment observed in AD are ultimately caused by the ensuing neuronal damage and synaptic dysfunction as demonstrated in Figure 1.

This figure depicts the key interconnected biological events underlying the initiation and progression of AD. Sustained neuroinflammation driven by activated microglia and astrocytes results in the release of pro inflammatory cytokines ROS and other inflammatory mediators that collectively contribute to neuronal damage. Persistent inflammatory signaling promotes abnormal tau hyperphosphorylation and its aggregation into neurofibrillary tangles while simultaneously increasing amyloid beta Aβ production and hindering its clearance. The buildup of Aβ plaques and pathogenic tau further disrupts synaptic function reduces neuronal plasticity and induces mitochondrial impairment alongside heightened oxidative stress. Over time these interrelated pathological mechanisms converge to drive progressive synaptic deterioration neuronal loss and the cognitive decline characteristic of AD.

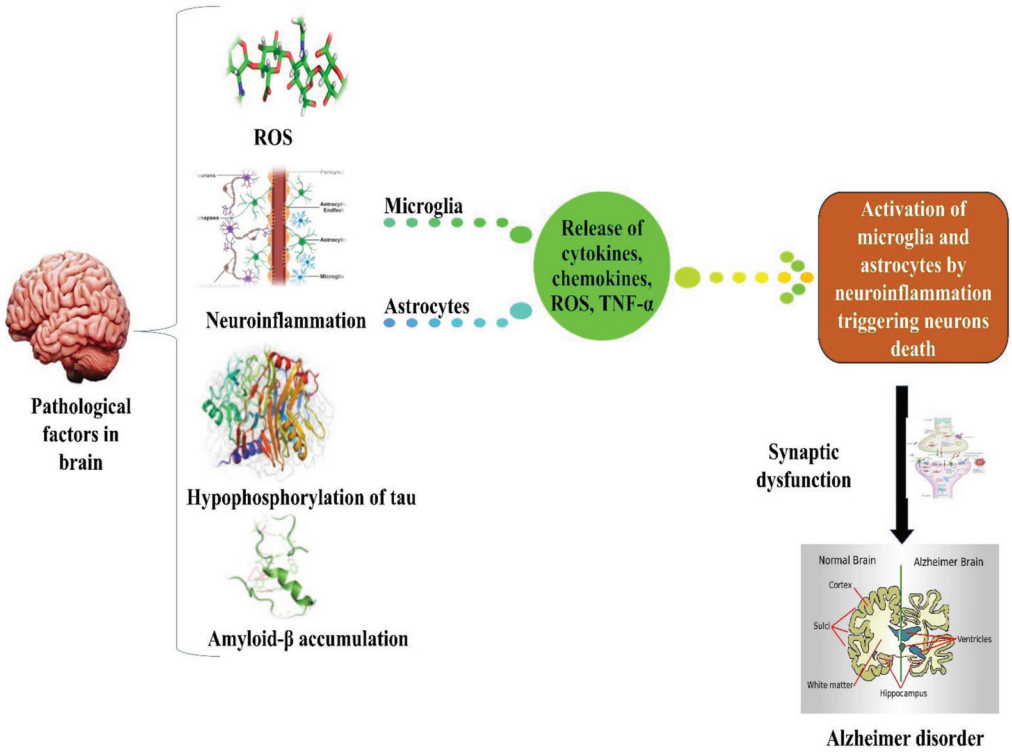


**Figure 1:** Pathophysiological Mechanisms Leading to AD

## 3. Pharmacological Interventions for Neuroinflammation in AD

The two primary types of AD therapy are symptomatic and disease modifying. Symptomatic therapies endeavor to restore cognitive function or manage neuropsychiatric symptoms without addressing the underlying biological factors that cause neuronal death. On the other hand disease modifying therapies are designed to change AD neuropathology in order to produce neuroprotection frequently via influencing a number of intermediary pathways (Olloquequi *et al.*, 2022).

Although existing AD drugs fail to show excellent clinical effectiveness many people have turned their focus to lifestyle changes for AD prevention and therapy. The 2022 AD report identifies high risk variables for all phases of the disease particularly insufficient exercise (Wang *et al.*, 2023). However vigorous exercise can also worsen inflammation by causing injured muscle to produce reactive nitrogen species and ROS lowering immunological function causing inflammation and depleting glycogen (Zhao, 2024).

Two novel drugs have been introduced more recently with the intention of delaying the progression of AD. These are aducanumab authorized by the FDA and sodium oligomannate approved in China. These drugs concentrate primarily on the cholinergic theory which was initially laid out by Davies and Maloney in 1976 and used for the moderate stages of AD (Davies, 1976).

Microglia can degrade Aβ plaques and provide neuroprotection in AD (Merighi *et al.*, 2022). Microglia also produce inflammatory cytokines in response to a variety of pathways including NFκB Akt mTOR p38 MAPK caspase nitric oxide and COX. The proliferator activated receptor PPARγ agonist pioglitazone decreases the inflammatory cytokine IL 1β and promotes the phagocytosis of Aβ (Ahmad *et al.*, 2019; Bagyinszky *et al.*, 2017). Specific COX 2 inhibitors such as celecoxib and rofecoxib also reduce neuroinflammation. The inflammatory mediators formed by microglia are also strongly inhibited by indomethacin a non selective COX inhibitor.

The mitophagy mechanism is believed to be extremely helpful in minimizing microglia induced inflammation because it encourages the phagocytosis of excess activated microglial cells and other inflammatory cells (Dhapola *et al.*, 2021). The development of TNF alpha synthesis inhibitors is another approach that is considered for AD (Belarbi *et al.*, 2012). Thalidomide and its derivatives commonly known as immunomodulatory imide medicines IMiDs block the generation of TNF alpha cytokines by targeting the 3′ untranslated region of TNF alpha mRNA. Currently

marketed IMiDs are good candidates for neurological diseases since they possess better blood brain barrier permeability and bioavailability than similar anti inflammatory drugs (Jung *et al.*, 2019).

Inflammatory diseases are increasingly being treated by targeting the NLRP3 inflammasome (Jiang *et al.*, 2020). Numerous strategies endeavor to decrease microglial cytokine production and prevent the NLRP3 inflammasome from activating (Zheng *et al.*, 2020). In order to reduce neuroinflammation oxidative stress and microglial activation several pharmaceutical interventions including NSAIDs glucocorticoids antioxidants cytokine inhibitors statins and PPARγ agonists function through different pathways. By focusing on these pathogenic pathways these drugs aim to protect neurons reduce disease progression and offer pharmacotherapeutic benefits for AD as shown in Figure 2.

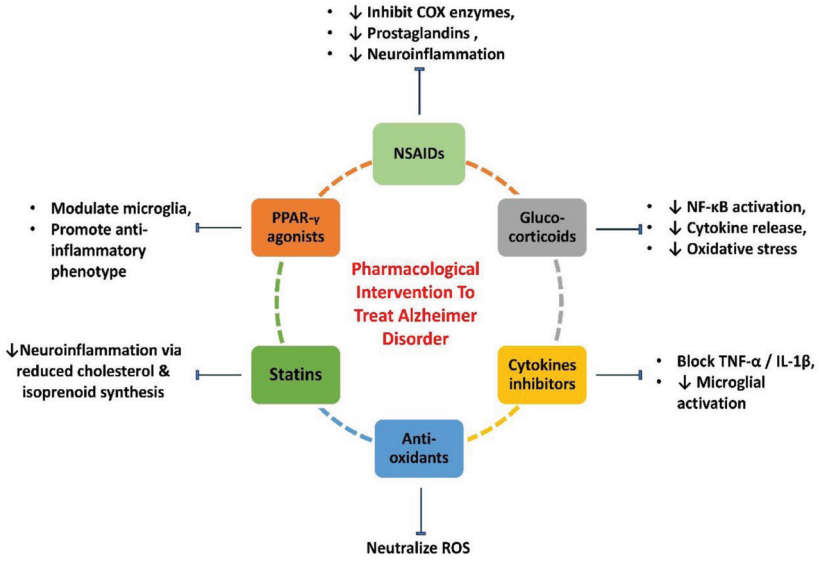


**Figure 2:** Pharmacological Strategies Targeting Neuroinflammation in AD

This figure provides an overview of therapeutic strategies designed to mitigate neuroinflammation in AD. It highlights key biological targets including activated microglia reactive astrocytes pro inflammatory cytokines and inflammasome associated signaling pathways. Moreover illustrated therapeutic classes such as NSAIDs corticosteroids cytokine inhibitors NLRP3 antagonists TREM2 targeting agents PPARγ agonists and naturally derived anti inflammatory compounds are shown to act through mechanisms that suppress inflammatory responses and support neuronal protection.

The intricacy of neuroimmune pathways in AD is illustrated by the broad range of treatment options that target neuroinflammation in the illness from NSAIDs and cytokine inhibitors to advanced techniques such as inflammasome blockers TREM2 agonists and senolytics. Translation into consistent clinical benefit remains a significant barrier despite the fact that numerous treatments show promise in preclinical and early clinical research. This highlights the need for precision based and synergistic therapy as shown in Table 1.

Moreover Table 1 provides a consolidated overview of emerging and established therapeutic interventions designed to modulate neuroinflammation in AD. It categorizes interventions based on their molecular targets mechanisms of action and reported outcomes across experimental and clinical contexts (Jiang *et al.*, 2020). By integrating diverse strategies from immune pathway inhibitors and metabolic modulators to microglial signaling targets the table highlights how multiple immunological nodes can be leveraged to counter pathological neuroinflammatory cascades (Juan *et al.*, 2019; Jurcău *et al.*, 2022).

**Table 1:** Therapeutic Strategies Targeting Neuroinflammation in AD

| Sr. No. | Strategy | Target Site | Mechanism | Therapeutic Agent | Outcomes | References |
|---|---|---|---|---|---|---|
| 1 | NSAIDs | COX-1/ COX-2, prostaglandin synthesis | Lower prostaglandin-mediated inflammation systemically and in brain (where BBB permeable) | Ibuprofen, naproxen (epidemiology; RCTs largely negative) | Reduced early epidemiologic signals of AD risk | (Rivers-Auty *et al.*, 2020) |

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| 2 | Corticosteroids / systemic immunosuppression | Glucocorticoid receptor (broad) | Broad suppression of cytokine production and immune activation | Prednisone, dexamethasone (not used chronically for AD) | Potent anti-inflammatory effect | (Shorey *et al.*, 2023) |
| 3 | Minocycline / tetracyclines | Microglial activation, MMPs, iNOS | Tetracyclines reduce microglial activation and inflammatory mediators | Minocycline (small trials / preclinical) | Preclinical benefit; small/heterogeneous clinical results | (Kim & Suh, 2009) |
| 4 | TNF-α blockade | TNF-α signaling | Neutralize TNF-α to reduce neurotoxic inflammation | Etanercept (perispinal reports), infliximab (experimental) | Anecdotal/small studies; mechanism plausible but robust trials lacking | (Torres-Acosta *et al.*, 2020) |
| 5 | IL-1β pathway inhibitors | IL-1β / IL-1R | Block IL-1–mediated neuroinflammation | Anakinra (IL-1R antagonist) — off-label / small studies | Implicated IL-1β | (Kitazawa, 2011) |
| 6 | JAK-STAT / IL-6 pathway inhibitors | JAK-STAT / IL-6 signaling | Prevent pro-inflammatory transcriptional responses downstream of cytokines | Tocilizumab (anti-IL6R), small-molecule JAK inhibitors (experimental) | JAK/STAT implicated in microglial responses | (Rusek *et al.*, 2023) |
| 7 | NLRP3 inflammasome inhibitors | NLRP3 inflammasome (microglia) | Prevent activation of caspase-1 → IL-18 / IL-1β release and pyroptosis | MCC950 (preclinical), OLT1177/ dapansutrile (clinical for other indications) | Strong preclinical rescue of AD phenotypes; MCC950 used preclinically and as a scaffold for clinical candidates | (Yin *et al.*, 2018) |
| 8 | TREM2 modulation (agonists) | TREM2 receptor on microglia | Stimulate microglial phagocytosis, survival, and Aβ clearance; alter inflammatory phenotype | AL002 (Alector) — TREM2 agonist antibody (Phase 1 → Phase 2 INVOKE program) | TREM2 is genetically validated (risk variants); AL002 showed target engagement, but INVOKE-2 failed to slow clinical decline — highlights complexity/ timing | (Schlepckow *et al.*, 2023) |
| 9 | C5a receptor (C5aR1) antagonists | C5aR1 (microglia/ astrocytes) | Block C5a-mediated chemoattraction and pro-inflammatory signaling | PMX205/PMX53 (preclinical); small-molecule antagonists (preclinical) | C5aR1 antagonism reduces gliosis, plaque burden, and cognitive deficits in multiple AD mouse models | (Gomez-Arboledas *et al.*, 2022) |
| 10 | Complement C3 / CR3 modulation | C3 activation products, CR3 receptor | Reduce opsonization and microglial phagocytosis of synapses | C3 inhibitors (research stage) | Cascade influences synaptic pruning in aging and AD | (Daborg *et al.*, 2012) |
| 11 | CD33 / Siglec-3 inhibitors | CD33 (microglial inhibitory receptor) | Block inhibitory signals that limit microglial Aβ clearance | Experimental antibodies/ small molecules (preclinical) | CD33 variants associate with AD risk; targeting aims to restore microglial clearance function | (Zhao, 2019) |
| 12 | P2X7 receptor antagonists | P2X7 (ATP receptor on microglia) | Prevent ATP-driven inflammasome activation and cytokine release | P2X7 antagonists — preclinical/early clinical | P2X7 drives NLRP3 activation; inhibitors reduce neuroinflammation in models | (Illes *et al.*, 2019) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 13 | α7 nicotinic acetylcholine receptor agonists | α7-nAChR (neurons & immune cells) | Activate cholinergic anti-inflammatory pathway; modulate microglial cytokine release | GTS-21 (encenicline — earlier trials), other agonists | Cholinergic anti-inflammatory pathway is a plausible route to dampen neuroinflammation | (Hoskin, 2019) |
| 14 | S1P receptor modulators (e.g., fingolimod) | S1P receptors on lymphocytes & glia | Modulate immune cell trafficking and microglial function | Fingolimod (approved for MS) — repurposing/ preclinical AD studies | Preclinical studies show reduced neuroinflammation and improved cognition in AD models | (McGinley & Cohen, 2021) |
| 15 | PPARγ agonists (anti-inflammatory metabolic shift) | PPARγ nuclear receptor (microglia, astrocytes) | Switch microglia to an anti-inflammatory/ metabolic phenotype | Pioglitazone (mixed trials), other PPARγ modulators | Metabolic reprogramming reduces inflammation; clinical trials mixed/negative in symptomatic AD | (Landreth *et al.*, 2008) |
| 16 | p38 MAPK inhibitors (e.g., neflamapimod) | p38 MAPK (inflammatory signaling in neurons/glia) | Reduce pro-inflammatory kinase signaling and cytokine production | Neflamapimod (clinical trials in AD/MCI) | Some biomarker and cognitive signals in early studies; mechanism targets neuroinflammatory kinase cascades | (Prins *et al.*, 2021) |
| 17 | JAK inhibitors (small molecules) | JAK kinases (downstream of many cytokines) | Broadly suppress cytokine-driven transcriptional responses | Tofacitinib/ ruxolitinib (repurposing interest) — preclinical/early exploration | JAK/STAT contributes to glial inflammatory response; potential for repurposing | (Al-Kuraishy *et al.*, 2025) |
| 18 | Nrf2 activators / antioxidant pathway | Nrf2 transcription factor (antioxidant response) | Upregulate antioxidant genes; indirectly reduce inflammasome activation | Dimethyl fumarate (approved in MS), bardoxolone (experimental) | Nrf2 activation reduced oxidative stress and inflammation in preclinical AD models | (Sidiropoulou *et al.*, 2023) |
| 19 | Senolytics (clear senescent glia) | Senescent cells (p16/p21 markers) | Remove senescent astrocytes/microglia that secrete inflammatory SASP | Dasatinib + quercetin (preclinical), other senolytics (preclinical/early) | Clearing senescent cells reduced inflammation and cognitive decline in models | (Alshaebi *et al.*, 2025) |
| 20 | Resolvin / pro-resolving lipid mediators (omega-3 derivatives) | Resolution pathways (ALX/FPR2, etc.) | Promote active resolution of inflammation rather than suppression | Resolvins, protectins, EPA/DHA supplementation (clinical & preclinical) | Pro-resolving mediators reduced chronic neuroinflammation in models; human evidence mixed | (Fiala *et al.*, 2015) |
| 21 | Microbiome / gut–brain immunomodulation | Gut microbiota → systemic immune signaling | Modulate peripheral inflammation that influences brain immune tone | Probiotics, dietary interventions, fecal microbiota modulation (research) | Gut microbes can modulate systemic inflammation and microglial states in animal models | (Zhang *et al.*, 2025) |
| 22 | Galectin-3 inhibitors | Galectin-3 (microglia/ astrocyte mediator) | Reduce pro-inflammatory and fibrosis-like responses | TD139/GB1107 (research stage) | Galectin-3 upregulated in neuroinflammation; inhibitors show benefit in models | (Tan *et al.*, 2021) |

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|---|---|---|---|---|---|---|
| 23 | HDAC inhibitors (epigenetic anti-inflammatory) | Histone deacetylases (epigenetic regulators) | Modulate transcription of inflammatory genes; promote neuroprotective programs | Valproate (non-selective), more selective HDAC inhibitors (preclinical) | Epigenetic modulation can reprogram glial inflammatory responses in models | (Hull *et al.*, 2016) |
| 24 | IVIG / immunomodulatory antibodies | Polyclonal IgG / Fc-mediated modulation | Broad immunomodulation, Fc receptor engagement, possible Aβ binding | IVIG trials in AD (largely negative) | IVIG modulate inflammation and clear Aβ | (Dodel *et al.*, 2010) |
| 25 | Anti-amyloid antibodies (indirectly modulate inflammation) | Amyloid-β plaques (amyloid clearance) | Removal of Aβ reduces plaque-associated inflammatory activation | Aducanumab, lecanemab — approved/ conditional; many others in trials | Anti-Aβ mAbs reduce plaques and alter local inflammation | (Piazza *et al.*, 2013) |
| 26 | Vaccination / active immunotherapy vs. inflammatory mediators | Induce antibodies vs. cytokines/ immune targets (conceptual) | Elicit immune response that neutralizes pathological inflammatory mediators | Experimental vaccines (research stage) | Conceptual and early preclinical work only for many neuroinflammation targets | (Mahdiabadi *et al.*, 2022) |
| 27 | CCR2 / chemokine signaling blockade | CCR2, CCL2 chemokine axis (monocyte recruitment) | Reduce peripheral immune cell infiltration and pro-inflammatory signaling in brain | CCR2 antagonists (preclinical) | Chemokine axes recruit peripheral cells that may exacerbate CNS inflammation | (Bose & Cho, 2013) |
| 28 | Chaperone / lipid metabolism modulators (TREM2-related lipid handling) | Lipid sensing/ transport in microglia (APOE/ TREM2 pathways) | Improve microglial lipid metabolism to reduce inflammatory phenotype | Approaches targeting APOE lipidation, progranulin modulators (clinical/preclinical) | Lipid metabolism in microglia intersects with inflammation and TREM2 signaling; progranulin drugs in development | (Li *et al.*, 2022) |
| 29 | BBB modulators / targeted delivery of immunomodulators | BBB permeation | Enhance delivery of antibodies/small molecules to brain to improve central anti-inflammatory action | BBB shuttles, receptor-mediated carriers (preclinical/clinical development) | Better CNS delivery for many biologics (e.g., TREM2 antibodies) | (Wei *et al.*, 2025) |

## 4. Novel Drug Delivery and Nanotechnology for AD

Nanotechnology, in conjunction with pharmaceuticals, helps to overcome many obstacles faced by potential drugs in treating neurodegenerative illnesses, such as AD (Karthivashan *et al.*, 2018). Treatment options are limited primarily by the drug's low oral solubility or inability to pass through the BBB, as demonstrated in Figure 3 (Khalin *et al.*, 2014). Many techniques have been developed to cross the BBB, including drug delivery systems, nanoparticles (NPs), nanoemulsions, solid lipid NPs (SLNs), and solid lipid carriers (Oesterling *et al.*, 2014; Sainsbury *et al.*, 2014). Pharmacotherapeutic failure can be caused by a drug's physicochemical properties, such as lipophilicity or hydrophilicity, ionization, extensive metabolization, inadequate bioavailability, large molecular weight, and side effects (Fonseca-Santos *et al.*, 2015). These constraints can be eradicated by using intranasal administration, which provides an alternate, non-invasive method of drug delivery to the brain via BBB bypassing and direct transport of drugs to the CNS (Kumar *et al.*, 2018; Zhang *et al.*, 2022). Overall, the integration of nanotechnology with conventional drug therapy offers a synergistic effect by enhancing bioavailability, targeted delivery, and therapeutic efficacy while minimizing systemic toxicity, as explained in Table 2 and demonstrated in Figure 3.

This figure highlights the therapeutic advantages of nanotechnology based approaches in AD treatment. Such nanoformulations can enhance drug transport across the BBB, enable targeted delivery to affected neuronal regions, and provide controlled drug release profiles. In addition, they help reduce systemic toxicity, improve drug stability, and facilitate the codelivery of multiple therapeutic molecules to achieve synergistic therapeutic effects.

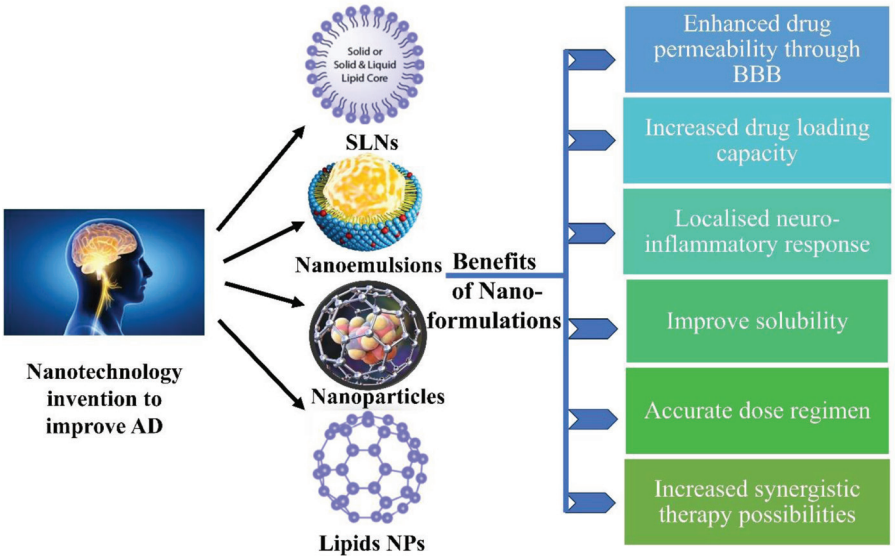


**Figure 3:** Salient Advantages of Nanotechnology to Treat AD

**Table 2:** Nanoformulations to Treat AD Induced by Neuroinflammation

| Sr. No. | Nanoformulations | Therapeutic agent | Particle size (nm) | Zeta potential (mV) | Polydispersity index | Entrapment efficiency (%) | Outcome | Ref(s) |
|---|---|---|---|---|---|---|---|---|
| 1 | SLN | Metformin | <200 | _ | _ | 94.08 | Decreased pyknotic neurons in hippocampus, neuronal injury | (Kumar *et al.*, 2023) |
| 2 | NPs | Rosiglitazone | 124.6 ± 12 | −17.5 ± 5.54 | 0.242 | 70.65 ± 5 | Increased brain permeability and provided targeted drug delivery | (K. C. Kakoty, Marathe, *et al.*, 2021) |
| 3 | Poly (lactic co glycolic acid) (PLGA) NPs | Ginsenoside Rg3 | 115 | _ | 0.081 | 70 | Increased solubility and improved neuroinflammation condition | (Aalinkeel *et al.*, 2018) |
| 4 | Nanoemulsion | Empagliflozin | 136.1 | −23.9 | 0.281 | _ | Promising anti-inflammatory efficacy | (Alhakamy *et al.*, 2024) |
| 5 | NPs | Rosiglitazone and vorinostat | 88 ± 12 | −24.1 ± 5 | 0.331 | 44.74–98.65 | Synergistic improved neuroprotective efficacy | (K. C. Kakoty, Krishna, *et al.*, 2021) |
| 6 | NPs | α-Mangostin | 94.26 ± 4.54 | −32 ± 0.43 | _ | 50.47 ± 1.96 | Improved therapeutic efficacy in AD | (Yao *et al.*, 2016) |
| 7 | NPs | Aloe vera coated curcumin | 76.12 | 6.27 ± 0.65 | 0.313 ± 0.02 | 90–95 | Provided safe and effective response | (Sharma *et al.*, 2024) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 8 | NPs | Resveratrol Selenium | 60–90 | _ | _ | _ | Modulate signaling pathways | (Abozaid *et al.*, 2022) |
| 9 | NPs | Auranofin | 101.5 ± 10.3 | _ | 0.438 ± 0.12 | 98 | Induced positive neuromodulatory effect | (Kushawaha *et al.*, 2024) |
| 10 | Lipid based NPs | Artesunate | 83.20 ± 12.0 | 16.65 ± 1.9 | 0.1 ± 0.02 | 81.8 ± 7.8 | Reduced Aβ Tau levels, rescuing hippocampal neurons, and improved cognitive functioning | (Attia *et al.*, 2025) |
| 11 | PLGA NPs | Auranofin | 101.5 ± 10.3 | 27.5 ± 5.10 | 0.438 ± 0.12 | 98 | Increased BBB permeability, triggered inflammatory agents | (Kushawaha *et al.*, 2025) |
| 12 | SLNs | Chrysin | 240.0 ± 4.79 | –40.4 ± 2.54 | _ | 86.29 ± 3.42 | Improved AD therapy | (Vedagiri & Thangarajan, 2016) |
| 13 | Nanoemulsion | Piracetam and Shatavarin | 183.6 | –20.05 ± 1.03 | 0.194 | _ | Enhanced targeted drug delivery and bioavailability | (Nadeem *et al.*, 2025) |
| 14 | NPs | Silibinin Albumin | 88–105 | _ | _ | 94.72 | Improving anti-inflammatory and antioxidant efficacy | (Pan *et al.*, 2021) |

Table 2 compiles recent nanotechnology based formulations evaluated for alleviating neuroinflammation in AD. It outlines key physicochemical attributes, therapeutic agents, and biological outcomes, highlighting how tailored nanosystems enhance brain delivery, improve neuroprotective efficacy, and overcome limitations associated with conventional drug administration (Sierksma *et al.*, 2020; Thakur *et al.*, 2023).

## 5. Clinical and Translational Challenges

The National Institute on Aging and the Alzheimer's Association established a research strategy that uses pathologic tau, neurodegeneration AT(N) biomarkers, and Aβ accumulation to characterize the biology of AD (Jack *et al.*, 2018). The three primary biomarkers include blood, cerebrospinal fluid, and imaging biomarkers. In order to identify both structural and functional brain activity in vivo, molecular imaging methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are used frequently (Mahaman *et al.*, 2022). In particular, 18 fluorodeoxyglucose induced entorhinal cortex atrophy and hippocampus in the medial temporal lobe is assessed by structural MRI (sMRI), PET imaging reveals tau and Aβ buildup, and PET indicates decreased glucose metabolism in the temporoparietal and posterior cingulate lobes (Klyucherev *et al.*, 2022; Zhang *et al.*, 2024). Thus, despite significant advances in biomarker discovery and neuroimaging, translating these clinical insights into effective diagnostic and therapeutic strategies for AD remains a major challenge, as demonstrated in Table 3.

**Table 3:** Clinical Trial Conducted to Treat Neuroinflammation Induced AD

| NCT No. | Description | Study type | Phase | Sponsor | Year |
|---|---|---|---|---|---|
| NCT06745583 | Using an open label, exploratory, phase II, proof of concept clinical study to investigate the safety, tolerability, and effect of EI 1071 on neuroinflammation in individuals with mild, moderate, or severe AD | Interventional | Phase 2 | Elixiron Immunotherapeutics (Hong Kong) Ltd. | 2025 |

| | | | | | |
|---|---|---|---|---|---|
| NCT04786223 | The purpose of this research is to ascertain how well PET CT imaging measures inflammation in the brain and how it relates to AD | Interventional | Phase 2 | Val Lowe et al. | 2025 |
| NCT04274998 | By employing PET Computerized Tomography imaging in individuals with AD, mild cognitive impairment, or healthy controls to provide better understanding of inflammation in the brain | Interventional | Early Phase 1 | University of Pennsylvania | 2025 |
| NCT05911178 | The goal of this work is to reassess how tau pathology, synaptic density, and microglial activation interact. AD patients will be paired with controls in a comparative, interventional, controlled, non randomized trial | Interventional | Not applicable | Centre Hospitalier St Anne | 2024 |
| NCT03958630 | The main goal is to determine if human patients with neurodegenerative disorders show varying levels of neuroinflammation in comparison to control subjects, as determined by brain uptake of a third generation [11C] ER176 TSPO ligand | Interventional | Phase 1 | National Institute of Mental Health | 2024 |
| NCT03548883 | The permeability through the BBB evaluated using a contrast enhanced brain MRI | Observational | _ | Advent Health | 2023 |
| NCT02377206 | The intention of the study is to evaluate the degree of neuroinflammation in patients with mild to moderate AD, as determined by the binding potential of [18F] DPA 714, and its association with the extent of cognitive loss throughout a 24 month follow up period | Interventional | Early Phase 1 | University Hospital | 2022 |
| NCT05378659 | The overall objective of this research endeavor is to detect the role of both pre existing neurodegenerative and neural inflammation pathology in the risk and etiology of postoperative cognitive dysfunction in 120 patients who undergo total knee arthroscopy | Observational | _ | University of Tennessee Graduate School of Medicine | 2022 |
| NCT01009359 | Radiation dosimetry in healthy volunteers and neuroinflammation patterns in potential Alzheimer's patients using PET imaging with DPA 714 BAY85 8102 F 18 | Interventional | Phase 1 | Bayer | 2013 |

Table 3 summarizes ongoing and completed clinical studies investigating neuroinflammation in AD using therapeutic interventions and advanced neuroimaging approaches. Moreover, these trials employ modalities such as PET based inflammation tracking, BBB permeability evaluation, and targeted immunomodulatory agents to assess safety, efficacy, and disease relevance in varied patient populations. Collectively, these findings aim to bridge mechanistic insights with clinically actionable diagnostic and therapeutic strategies.

## 6. Conclusion

AD remains one of the most challenging neurodegenerative conditions, with neuroinflammation emerging as a key mechanism that causes hyperphosphorylation, neuronal damage, and tau and amyloid beta accumulation. Activated astrocytes and microglia produce a variety of inflammatory mediators and cytokines that contribute to the cascade of neuronal death, synaptic dysfunction, and oxidative stress. Targeting these neuroinflammatory cascades has emerged as an addressing therapeutic approach for altering the condition rather than merely providing symptomatic relief. Recent advances have been explored, such as the use of natural anti-inflammatory drugs like NSAIDs and phytochemicals, the suppression of pro-inflammatory cytokines, regulation of eicosanoid and arachidonic acid pathways, and microglial modulation. However, despite encouraging preclinical findings, clinical translation is hampered by difficulties related to drug toxicity, poor selectivity, and blood–brain barrier penetration. Crucially, the majority of already marketed drugs only offer temporary symptomatic relief, and other novel therapies are currently failing in late-stage clinical studies because of inadequate effectiveness or safety issues. Current investigations emphasize multimodal therapeutic approaches that incorporate neuroprotective, antioxidant, amyloid/tau-modifying, and anti-inflammatory effects to

induce synergistic outcomes. Moreover, the development of sophisticated drug delivery strategies, such as intranasal formulations and nanocarriers, has the potential to improve anti-inflammatory drug brain targeting and help to overcome pharmacokinetic constraints. Overall, growing evidence suggests that addressing neuroinflammation is not merely an adjunctive avenue but also a crucial disease-modifying treatment approach in AD. Despite promising preclinical findings, most anti-inflammatory approaches have shown limited clinical translation. This is largely attributed to poor penetration across the blood–brain barrier, unintended systemic toxicity, variability in patient responses, and the frequent failure of candidates during advanced clinical trial phases. These limitations suggest that therapies aimed at modulating neuroinflammation should not be evaluated in isolation. Instead, their clinical relevance depends on understanding how inflammatory processes intersect with tau aggregation, amyloid deposition, synaptic dysfunction, and oxidative stress. Collectively, current evidence emphasizes the need for integrated, mechanism-oriented therapeutic strategies rather than solely symptom-driven interventions.

## 7. Future Perspectives

Despite substantial progress in understanding the role of neuroinflammation in AD, translating these pharmacological insights into effective clinical therapies remains a major challenge. Future investigations should prioritize delineating inflammatory pathways and their mechanistic association with tau pathology and amyloid beta progression, as this remains central to developing targeted interventions. Furthermore, identifying more selective molecular targets such as purinergic receptors, TREM2 signaling, fractalkine receptor pathways, and the NLRP3 inflammasome may offer refined therapeutic opportunities compared to broad-spectrum anti-inflammatory agents. Additionally, approaches such as immunotherapies, complement inhibitors, and PPAR agonists hold promise in shifting microglial function from a pro-inflammatory to a neuroprotective phenotype, representing an emerging therapeutic direction.

Moreover, intranasal delivery platforms, liposomal formulations, and nanotechnology-based carrier systems present promising avenues to enhance drug permeability across the BBB while reducing systemic toxicity. Multimodal therapeutic strategies combining anti-inflammatory agents with antioxidants, neurotrophic molecules, and amyloid/tau-modifying interventions are gaining prominence for overcoming the limitations of single-agent therapies. Similarly, biomarker-guided patient stratification, genetic profiling, and personalized therapeutic frameworks will be crucial to improving treatment responsiveness, particularly given the heterogeneous nature of AD. As a result, well-designed, long-term clinical studies that account for inter-patient variability, disease stage, and long-term safety are essential to translate preclinical insights into clinically meaningful outcomes. More comprehensive, large-scale investigations are required to validate these therapeutic strategies and determine their true disease-modifying potential in AD.

## Abbreviations

**AD**: Alzheimer's Disease; **NSAIDs**: Non-Steroidal Anti-Inflammatory Drugs; **CNS**: Central Nervous System; **NFT**: Neurofibrillary Tangles; **A**β: Beta-Amyloid; **FDA**: Food And Drug Administration; **GWAS**: Genome-Wide Association Studies; **IMiDs**: Immunomodulatory Imide Medicines; **BBB**: Blood–Brain Barrier; **NPs**: Nanoparticles; **SLNs**: Solid Lipid Nanoparticles; **PLGA**: Poly(Lactic-Co-Glycolic Acid); **PET**: Positron Emission Tomography; **MRI**: Magnetic Resonance Imaging; **CT**: Computed Tomography; **PPAR**: Proliferator-Activated Receptor.

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## Authorship Contribution

Kunal contributed to the study idea, design, data collection, and manuscript writing.

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This article is a review-based study and does not involve any experiments on human participants or animals. Therefore, ethical approval was not required.

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The author declares that this manuscript is original, has not been published previously, and is not under consideration for publication elsewhere. All relevant sources have been appropriately cited.

## Conflict of Interest

The author declares no conflict of interest.

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