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Review

Biomaterials-based anti-inflammatory treatment strategies for Alzheimer's disease

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From the Contents

Abstract

The current therapeutic drugs for Alzheimer's disease only improve symptoms, they do not delay disease progression. Therefore, there is an urgent need for new effective drugs. The underlying pathogenic factors of Alzheimer's disease are not clear, but neuroinflammation can link various hypotheses of Alzheimer's disease; hence, targeting neuroinflammation may be a new hope for Alzheimer's disease treatment. Inhibiting inflammation can restore neuronal function, promote neuroregeneration, reduce the pathological burden of Alzheimer's disease, and improve or even reverse symptoms of Alzheimer's disease. This review focuses on the relationship between inflammation and various pathological hypotheses of Alzheimer's disease; reports the mechanisms and characteristics of small-molecule drugs (e.g., nonsteroidal anti-inflammatory drugs, neurosteroids, and plant extracts); macromolecule drugs (e.g., peptides, proteins, and gene therapeutics); and nanocarriers (e.g., lipid-based nanoparticles, polymeric nanoparticles, nanoemulsions, and inorganic nanoparticles) in the treatment of Alzheimer's disease. The review also makes recommendations for the prospective development of anti-inflammatory strategies based on nanocarriers for the treatment of Alzheimer's disease.

Key Words: Alzheimer's disease; anti-inflammation; blood-brain barrier; drug delivery; microglia; nanoparticles; neuroinflammation; plant extracts

Introduction

As a typical neurodegenerative disease, Alzheimer's disease (AD) has an incidence of approximately 1.5% in older subjects aged ≥ 65 years, and its incidence increases by approximately 2-fold with every 5 years of age. AD is the most common type of dementia. Its onset is insidious and progressive. The main clinical manifestations are cognitive decline, mental symptoms, behavioral disorders, and the gradual decline of daily living ability. In the United States, AD had the 6th-highest death rate in 2021 (No authors listed, 2021). More than 50 million people worldwide currently suffer from dementia, and that number is expected to reach 150 million by 2050 (Alzheimer's Disease International, 2019). The annual global economic burden of dementia has already reached one trillion dollars, and this figure is set to rise rapidly owing to the impact of the coronavirus disease 2019 (COVID-19) pandemic (Alzheimer's Disease International, 2019; No authors listed, 2021). Therefore, AD has become a serious public health problem worldwide.

The etiology of AD is complex, and the main pathological changes are β-amyloid (Aβ) deposition, abnormal phosphorylation of Tau protein, neuron loss, and synaptic changes. Its pathogenesis has not been fully determined and may be caused by the interaction of multiple pathogenic factors, pathways, and molecular mechanisms. The main pathogenic hypotheses of AD occurrence and development include the Aβ hypothesis, Tau hypothesis, aging hypothesis, mitochondrial cascade hypothesis, blood-brain barrier (BBB) dysfunction, and the concept of the brain-gut axis (Swerdlow and Khan, 2009; Kritsilis et al., 2018; Huang et al., 2020; Rutsch et al., 2020; Garbuz et al., 2021; Roda et al., 2022; Wei et al., 2022). However, the single pathogenicity hypothesis cannot fully explain the complex pathological changes and clinical treatment difficulties of AD. Interestingly, neuroinflammation links the different AD hypotheses. Existing studies have confirmed that neuroinflammation is closely related to cognitive impairment, and neuroinflammation are throughout the entire disease progression of AD, and systemic inflammation including central and peripheral inflammation increases the pathological burden of AD and accelerates AD progression (de Oliveira et al., 2021; Garbuz et al., 2021). Unfortunately, the causal relationship between neuroinflammation and AD pathology is still unclear.

The current two major classes of drugs for the treatment of AD, such as cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, can improve the clinical symptoms of AD to some extent. However, they cannot terminate or reverse the disease process (No authors listed, 2021). Thus far, several studies have focused on the purpose of disease modification therapy by alleviating or reversing the pathological changes of AD (No authors listed, 2021). Aducanumab, a human Aβ-monoclonal antibody targeting aggregated Aβ, can alleviate Aβ plaque burden in the brains of both AD model mice and humans after intravenous administration. It has been approved by the U.S. Food and Drug Administration (FDA), but its safety and efficacy have not been unanimously recognized (Knopman et al., 2021). The recent phase III trial results of Ban2401 (Lecanemab), which targets soluble aggregated Aβ preferentially showed better efficacy and safety, and gained accelerated approval from the U.S. FDA on January 6, 2023 for the treatment of early AD (Larkin, 2023). Given the relationship between inflammation and pathological changes in AD, in addition to directly targeting typical pathological changes, inhibition of inflammation is considered an effective means for the prevention and treatment of AD (de Oliveira et al., 2021). On this basis, the bioavailability of anti-inflammatory agents that relieve the central inflammatory microenvironment can be improved by using biomaterials to achieve the purpose of significantly improving neuroinflammation and reducing the side effects of drugs (**Figure 1**; Tu et al., 2022). In this review, we discuss the fundamental links between neuroinflammation and the pathogenic hypotheses of AD and the anti-inflammatory strategies for AD, and evaluate the potential of anti-inflammatory strategies based on nanocarriers for the treatment of AD.

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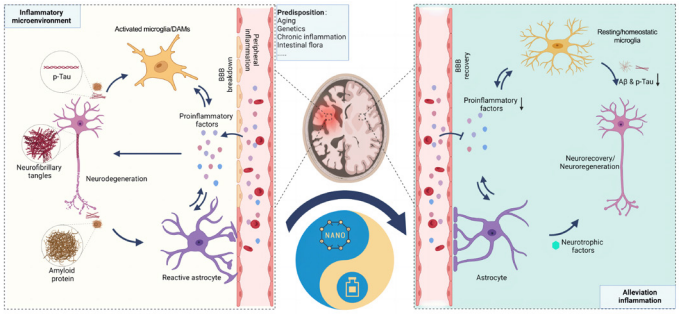

Figure 1 | **Nanocarrier-based anti-inflammatory therapeutics improve the inflammatory microenvironment in Alzheimer's disease.**
Created with BioRender.com. Aβ: Amyloid β-protein; BBB: blood-brain barrier; DAM: disease-associated microglia; p-Tau: phosphorylated Tau.

Retrieval Strategy

The authors conducted searches based on the PubMed database using subject terms from each section of the manuscript, such as Alzheimer's disease, Aβ, Tau, neuroinflammation, microglia, anti-inflammation, and nanoparticles either individually or in combination, and selected literature including clinical and preclinical studies. Most of the publications were from the last decade, and an earlier paper in 1990 was also cited for its enlightening value. We also accessed Alzforum (https://www.alzforum.org/) to identify the ongoing clinical trials on anti-inflammatory treatments for AD.

Neuroinflammation and Hypothesis of Alzheimer's Disease

Aβ and neuroinflammation

Aβ deposition is not only the main pathological change in AD but also the core biological marker of AD. Aβ deposition is closely associated with neuroinflammation. In the early stages of AD, the accumulation of reactive microglia around plaques and protofibrils can contribute to Aβ clearance and limit plaque growth and accumulation, thereby limiting their spread and preventing neurotoxicity (Condello et al., 2015; Keren-Shaul et al., 2017). Microglia associated with neurodegenerative diseases such as AD are termed disease-associated microglia (Paolicelli et al., 2022). With the progression of AD, microglial states in different spatiotemporal contexts exhibit unique and diverse phenotypic profiles such as the microglial neurodegenerative phenotype and activated response microglia, which is partly because of the possibility that Aβ can activate microglia in the form of fibrous plaques, protofibrils, and oligomers, thereby promoting neuroinflammation (Yates et al., 1999; Keren-Shaul et al., 2017; Krasemann et al., 2017; Jian et al., 2019; Hampel et al., 2021; LaRocca et al., 2021; Paolicelli et al., 2022). In *in vitro* experiments, $A\beta_{1-42}$ was shown to significantly stimulate the secretion of pro-inflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein (MCP)-1 from rat astrocytes and N9 microglia after co-incubation (Zhao et al., 2018).

Aβ oligomers can induce neuroinflammation and neurodegeneration by stimulating the release of pro-inflammatory factors and disturbing the synthesis of anti-inflammatory factors such as transforming growth factor-β1 from microglia (Jian et al., 2019; Torrisi et al., 2019). Aβ oligomers also increase the C1q enrichment at synapses, thereby mediating synaptic loss in early AD induced by phagocytic microglia (Hong et al., 2016a). Together with microglial activation, both $A\beta_{1-42}$ monomers/oligomers and $A\beta_{1-40}$ can play a cytokine-like role in promoting astrocyte activation and enhance neuroinflammatory responses (LaRocca et al., 2021). Neuroinflammation also promotes Aβ production. Pro-inflammatory factors secreted by microglia, especially TNF-α, IL-1β, and interferon (IFN)-γ, stimulate γ-secretase activity, resulting in increased synthesis of insoluble Aβ peptides and continual exacerbation of neuroinflammation (Liao et al., 2004). A recent study confirmed that pro-inflammatory factors enhance γ-secretase activity and increase Aβ deposition through interferon-induced transmembrane protein 3 (Hur et al., 2020). Hence, various aggregated forms of Aβ can act in conjunction with pro-inflammatory factors, leading to chronic activation of nuclear factor kappa B (NF-κB) and transcriptional activation of beta-secretase 1 (BACE1) in glial cells, in turn activating and enhancing the positive feedback loop of inflammation and ultimately causing chronic neuroinflammation (Bourne et al., 2007).

Tau protein and neuroinflammation

In the etiopathogenesis of AD, it is widely believed that neurofibrillary tangles caused by abnormally phosphorylated Tau proteins are downstream events of Aβ, which means that the conversion of Tau proteins from the normal to the toxic state is triggered by Aβ (Bloom, 2014). The particular mechanism is unknown, but Aβ leading to microglial activation and the release of pro-inflammatory cytokines are the possible triggers for induction and promotion of Tau phosphorylation, of which the nucleotide oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 inflammasome is an important component (Blurton-Jones and Laferla, 2006; Ising et al., 2019). Neuroinflammation can induce and exacerbate Tau pathology (Garbuz et al., 2021). Sterile inflammation-promoting lipopolysaccharide (LPS) induces Tau hyperphosphorylation in non-transgenic mice through Toll-like receptor 4 (TLR4) signaling activation in microglia; this process is facilitated by the genetic absence of IL-10 and the stimulation of IL-6 (Weston et al., 2021). Moreover, in the Aβ precursor protein (APP)/presenilin-1 (PS1)/Tau 3×Tg-AD mouse model, acute and chronic inflammation induced by intracranial injection of mouse hepatitis virus significantly exacerbates the Tau pathology and leads to impaired spatial memory (Sy et al., 2011). In addition, activated microglia promote intracranial dissemination of phosphorylated Tau, resulting in further aggravation of pathological changes in AD (Maphis et al., 2015). However, Tau protein can also activate microglia and enhance the inflammatory response. Microglial activation associated with Tau protein is observed in P301S, R406W, and P301L transgenic mice. Misfolded recombinant truncated Tau (151-391, 4R) induces mixed primary rat glial cultures to secrete inflammatory mediators such as pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), tissue inhibitors of metalloproteinase-1, and nitric oxide (NO) and activates rat primary microglia via mitogen-activated protein kinase (MAPK) and NF-κB pathways (Kovac et al., 2011).

Neuroinflammation in other hypotheses of AD

In addition to the two classical hypotheses, aging, mitochondrial dysfunction, BBB dysfunction, and even susceptibility genes of AD are closely associated with neuroinflammation. Aging is the most critical risk factor for AD, and accelerated aging significantly exacerbates Aβ deposition in the brain and cognitive impairment in AD patients (Lok et al., 2013; Kritsilis et al., 2018). The accumulation of senescent cells in the central nervous system (CNS) as a presumed causative mechanism of AD is thought to contribute to the progression of AD. One possible reason for this is the reduced physiological function of senescent neuronal and glial cells, and another is the senescence-associated secretory phenotype, which consists of active secretion of paracrine factors by senescent cells. Senescence-associated secretory phenotype involves a variety of inflammatory factors, chemokines, and growth factors-among which many pro-inflammatory cytokines such as IL-1, IL-6, and IL-8 directly cause and exacerbate neuroinflammation. Furthermore, senescence-associated secretory phenotype induces paracrine senescence, which leads to the persistence of central neuroinflammation (Kritsilis et al., 2018; Lopes-Paciencia et al., 2019).

Some investigators have proposed the mitochondrial cascade hypothesis, suggesting that in sporadic AD, mitochondrial dysfunction is an event that parallels or even precedes Aβ deposition. Decreased mitochondrial function is believed to be a feature of cellular senescence and is directly related to Aβ production and Tau phosphorylation (Kritsilis et al., 2018). Based on this foundation, mitochondrial dysfunction accelerates neuronal impairments caused by pathological factors such as Aβ and Tau. One reason for this is the neuroinflammatory response generated by the NLRP3 inflammasome and cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase/stimulator of INF genes signaling pathways activated by declining mitochondrial function (Bader and Winklhofer, 2020).

Disruption of the integrity of the BBB plays an important role in the pathogenesis of AD (Bowman et al., 2018; Huang et al., 2020). A wide range of conditions, including Aβ, aging, chronic neuroinflammation, peripheral inflammation, and dysbiosis of the intestinal flora have been shown to contribute to BBB dysfunction (Zhang et al., 2017b; Huang et al., 2020; Rutsch et al., 2020). BBB dysfunction not only facilitates the entry of toxic peripheral plasma components—including inflammatory factors and bacterial products, and peripheral immune cells—into the brain but also reduces the entry of oxygen and other neuro-nutrients into the brain, thus diminishing the efflux of Aβ from the CNS (Bowman et al., 2018; Huang et al., 2020). All of these factors contribute to the persistence of neuroinflammation and form a vicious cycle that drives disease progression in AD.

Several genes associated with AD development are involved in neuroinflammation. Allele E4 of the apolipoprotein E (*ApoE4*) has been shown to be associated with an increased risk of AD. ApoE4 was also associated with a higher innate immune response, implying that carriers have a higher inflammatory response to stressors (Vitek et al., 2009). In addition, genome-wide association studies have shown that several other genes associated with increased risk of AD, such as *TREM2*, *CD33*, *CLU*, *CR1*, *EPHA1*, *ABCA7*, *MS4A4A*/*MS4A6E*, and *CD2AP*, are also involved in regulating the clearance of misfolded proteins by the microglia and can directly or indirectly promote neuroinflammation (Ozben and Ozben, 2019).

Laboratory tests and imaging studies also reveal direct evidence of neuroinflammatory dysregulation in AD. Pro-inflammatory factors such as IL-1β, IL-6, and TNF-α in blood samples and pro-inflammatory mediators such as TNF-α, MCP-1, chitinase-3-like protein 1, and IL-8 in cerebrospinal fluid samples are significantly higher in mild cognitive impairment and mild AD groups than in control groups (Motta et al., 2007; Swardfager et al., 2010; Dursun et al., 2015; Chen et al., 2018; Taipa et al., 2019). Positron emission tomography imaging measures a putative inflammatory biomarker—translocator protein 18 kDa—suggesting its increased expression in the brains of AD patients (Chaney et al., 2019).

Neuroinflammation and neuronal injury

All the above pathogenic mechanisms ultimately lead to the chronicity of neuroinflammation. Chronic neuroinflammation is the main factor leading to neuronal death, mainly due to the neurotoxic microenvironment formed by pro-inflammatory cytokines, chemokines, and matrix metalloproteinases

(Moyse et al., 2022). A recent study also revealed that weakly chronic inflammation is the major contributor to neuronal loss in the neuronal microenvironment of AD, and there are potential interactions between its signal transduction and neuronal apoptotic signaling pathways (Li et al., 2022a). Apoptotic neurons also recruit homeostatic microglia and induce them to convert to the microglial neurodegenerative phenotype in AD, further exacerbating Aβ deposition and neuritic dystrophy (Krasemann et al., 2017). The cross action between neuroinflammation and neural injury eventually results in the ongoing loss of neurons and synapses and promote the development of clinical symptoms of AD.

Anti-Inflammatory Strategies for Alzheimer's Disease

Small molecule drugs

Nonsteroidal anti-inflammatory drugs

A case-control study conducted in 1990 showed a significantly lower incidence of AD in patients with rheumatoid arthritis aged > 64 years, and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) was cited as one of the underlying causes (McGeer et al., 1990). A systematic review and meta-analysis based on six cohort studies and three case-control studies in 2003 concluded that NSAIDs have a significant protective effect against AD (Etminan et al., 2003). Cyclooxygenase (COX) is one of the major contributors to neuroinflammation, and NSAIDs are generally thought to exert anti-inflammatory effects by inhibiting COX. However, current studies suggest that not all NSAIDs are protective against AD. Randomized multicenter clinical trials have shown that selective COX2 inhibitors (rofecoxib) or traditional non-selective NSAIDs (naproxen) do not mitigate cognitive decline in patients with mild-to-moderate AD in the early and subsequent follow-up (Aisen et al., 2003; ADAPT Research Group et al., 2007). Similarly, there was no evidence that aspirin was effective in reducing the risk of dementia, mild cognitive impairment, or cognitive decline over a median 4.7-year follow-up in another study (Ryan et al., 2020). Animal studies have also shown that ibuprofen, indomethacin, and flurbiprofen can reduce $A\beta_{42}$ levels by inhibiting γ-secretase activity, while other NSAIDs, including naproxen and aspirin, do not have this kind of effect (Weggen et al., 2001; Eriksen et al., 2003). This appears to be consistent with the results of the above clinical studies.

Interestingly, aspirin has shown different results in animal and clinical studies (Eriksen et al., 2003; Wang et al., 2015; Chandra et al., 2018; Ryan et al., 2020; Weng et al., 2021). In 2015, a meta-analysis showed that aspirin users, especially long-term users, had a lower risk of AD than non-users (Wang et al., 2015). A recent prospective cohort study indicated that AD patients who used aspirin at the baseline had slower cognitive decline over time than those who did not (Weng et al., 2021). In the laboratory, after 22 hours of coculture with primary mouse astrocytes and 1 month of oral administration to the 5xFAD mouse model, aspirin alleviated the Aβ burden by inducing peroxisome proliferator-activated receptor-α to enhance lysosomal activity (Chandra et al., 2018). Accordingly, a considerable proportion of NSAIDs should be able to protect against AD through other anti-inflammatory targets, and some NSAIDs have the promising protective effect of AD. In one study, animal experiments showed that ibuprofen reduced IL-1β levels in the brains of Tg2576 mice, significantly depressed microglial activation, and attenuated Aβ pathological burden (Lim et al., 2000). Ibuprofen can increase the efflux of Aβ to treat AD by inhibiting the expression of inflammatory mediators such as TNF-α, IL-1β, IL-6, and NF-κB to up-regulate P-glycoprotein levels (Zhang et al., 2018). Additionally, ibuprofen is involved in regulating neuronal plasticity by upregulating norepinephrine and dopamine gene expression levels and downregulating the neuronal tryptophan 2,3-dioxygenase (Tdo2) gene to counteract the neurotoxic influence of early accumulation of Aβ oligomers (Woodling et al., 2016). In addition to ibuprofen, indomethacin improves neuroinflammation and memory impairment in AD by inhibiting C-terminal caspase recruitment domain domain-containing protein 4 and NLRP3 inflammasome-related genes, and reducing IL-1β and caspase-1 (Karkhah et al., 2021). High doses (30 mg/kg) of nitric oxide donor-containing flurbiprofen are effective in reducing Aβ burden and decreasing microglia activation around plaques (van Groen et al., 2011).

Although the vast majority of clinical trials on NSAIDs for the treatment of AD have been terminated given their poor efficacy or severe side effects, ibuprofen is in a phase III clinical trial (NCT02547818). It has been recently demonstrated that targeting peripheral or central prostaglandin E receptor 2 to block the prostaglandin E2 signaling pathway can improve systemic and neuroinflammation and reverse cognitive aging (Minhas et al., 2021), which indicates that COX and its downstream nodes are crucial targets for AD therapy. Therefore, NSAIDs possess the potential to be used for AD treatment. Extensive well-designed pre-clinical and clinical trials are needed to evaluate the preventive and therapeutic effects of different NSAIDs on AD in different populations, to obtain more evidence-based clinical results. In addition to specific anti-inflammatory mechanisms, specific drug selection for NSAIDs, time to initiate intervention, duration of management, and even baseline characteristics of the subjects (e.g., *ApoE* mutation) as well as patient sensitivity and tolerance to NSAIDs may lead to different outcomes (Pasqualetti et al., 2009; O'Bryant et al., 2018).

Neurosteroids

Numerous clinical and epidemiological studies have supported sex-related differences in the prevalence, risk, and severity of AD. It is hypothesized that this is because of decreased sex hormones or elevated follicle-stimulating hormone in women with late-onset AD (Xiong et al., 2022). A study in multiple AD mouse models supports the higher susceptibility of female patients to AD. Female 3×Tg-AD mice over 12 months of age suffer from more pronounced Aβ plaque load, more pronounced neurofibrillary tangle aggregation and intense hippocampal neuroinflammation, and worse cognitive behavior (Yang et al., 2018a). Ovariectomy increases the expression of pro-inflammatory factors IL-1β, IL-18, and NLRP3 in the hippocampus of normal female mice (Xu et al., 2016b). Moreover, intracerebroventricular (ICV) injection of Aβ induces higher NF-κB signaling activation, more severe Aβ accumulation, and memory impairment in ovariectomized mice compared to controls (Yun et al., 2018). Estrogen supplementation can reduce neuroinflammation to some extent. *In vitro*, β-estradiol inhibits NF-κB activation in microglia (BV-2 cells), thereby reducing neuroinflammation and preventing Aβ-induced cell death of primary neurons (Yun et al., 2018). *In vivo*, 17β-estradiol intraperitoneal administration improves d-gal-induced oxidative stress and neuroinflammation in male mice and downregulates BACE1 and Aβ protein expression in the brain, improving mouse behavior (Khan et al., 2019). This is because estrogen can activate sirtuin1 (SIRT1) and its downstream signaling either indirectly (binding to estrogen receptor (ER)α) or directly (allosteric regulation) (Khan et al., 2019).

Although multiple prospective clinical trials and meta-analyses of estrogen replacement therapy in perimenopausal women have not reached consistent conclusions, a considerable body of research supports estrogen replacement therapy as an option for the prevention and treatment of AD (Gleason et al., 2015; Xu et al., 2016a; Yu et al., 2020). However, long-term supplementation with non-selective estrogens that activate ERα may increase the risk of breast cancer and endometrial carcinoma, so selective ERβ agonists may be a better choice than non-selective estrogens (Yan et al., 2022). The synthetic ERβ agonist tibolone and diarylpropionitrile significantly attenuate the palmitic acid-induced inflammatory response of BV-2 cells (Hidalgo-Lanussa et al., 2018). Patchouli alcohol can reduce neuronal oxidative stress by targeting ERβ, increasing peroxidase expression, and activating the ERβ/brain-derived neurotrophic factor/tyrosine protein kinase B/cyclic AMP-response element binding protein pathway to maintain synaptic function (Yan et al., 2022). Furthermore, activation of the ERβ receptor in the early stage of AD can also modulate microglial function to promote Aβ clearance and improve cognitive function (Yan et al., 2022), but the specific mechanism needs to be further studied.

Progestin, a neurosteroid (i.e., endogenous steroids synthesized inside the nervous tissue), is also believed to have neuroprotective effects, and reactive glial cells may be the target of its anti-inflammatory effects (De Nicola et al., 2013). Progesterone decreases the expression of inflammatory genes (*IL-1β*, *TNF-α*, *TLR4*, and *NLRP3*) associated with neuroinflammation, increases the antioxidant capacity of the hippocampus, and diminishes lipid peroxidation in mouse models of maternal separation stress (Nouri et al., 2020). Progesterone pretreatment attenuates LPS-stimulated TNF-α, inducible nitric oxide synthase (iNOS), and COX2 expression in BV-2 microglia in a dose-dependent manner and exhibits pleiotropic anti-inflammatory effects by down-regulating pro-inflammatory mediators corresponding to the inhibition of NF-κB and MAPK activation (Lei et al., 2014). Progesterone also inhibits Aβ-induced neuroinflammatory response in astrocytes by suppressing NLRP3 inflammasome activation and the double-stranded RNA-dependent protein kinase-like endoplasmic reticulum kinase/eukaryotic initiation factor 2α-dependent endoplasmic reticulum stress (Hong et al., 2016b, 2019). In an animal experiment, progesterone injected subcutaneously blocked the neuroinflammation mediated by intracranial injection of $A\beta_{25-35}$ in a dose-dependent manner, reversed the upregulation of TNF-α and IL-1β, increased hippocampal pyramidal cell survival, and improved cognitive levels (Liu et al., 2013a). However, not all progestins improve cognitive function. In the water radial arm maze and Morris water maze experiments of ovariectomized middle-aged rats, levonorgestrel supplementation enhanced learning, while norethindrone acetate and medroxyprogesterone acetate impaired learning and memory (Braden et al., 2017). Future studies are expected to elucidate the mechanisms of different structures of progestins and their interactions with other sex hormones.

Low plasma testosterone levels are also significantly associated with AD in older men (Lv et al., 2016). Patients with prostate cancer who received androgen deprivation therapy have an increased risk of developing dementia or AD compared to those who did not receive androgen deprivation therapy, and this was more pronounced when the duration of treatment was longer than 12 months (Sari Motlagh et al., 2021). Androgens (testosterone and dihydrotestosterone [DHT]) enhance $A\beta_{42}$ uptake by microglia through upregulation of formyl peptide receptor 2, increase $A\beta_{42}$ degradation through induction of endothelin-converting enzyme 1c, and decrease $A\beta_{42}$-induced pro-inflammatory cytokine production through inhibition of $p38^{MAPK}$ and NF-κB activation (Yao et al., 2017). DHT also inhibits LPS-induced pro-inflammatory mediator release (TNF-α, IL-1β, IL-6, iNOS, COX2, NO, and prostaglandin E2) from BV-2 cells and primary microglia by blocking the TLR4-mediated NF-κB and $p38^{MAPK}$ signaling pathways, thereby protecting human neuroblastoma cells (SH-SY5Y) from inflammatory injury (Yang et al., 2020). In addition, supplementation with exogenous DHT ameliorates LPS-induced chronic neuroinflammation when exacerbated by endogenous DHT depletion in castrated mice. Moreover, DHT can modulate the mRNA levels of anti-inflammatory cytokines (IL-10 and IL-13)—as well as the expression of Aβ, apoptotic proteins (caspase-3, Bcl-2, and Bax), and synaptophysin in the brain—and improve spatial learning and motor deficits (Yang et al., 2020).

Appropriate neurosteroid supplementation has high therapeutic potential

for the prevention and treatment of AD, but hormone replacement therapy for AD is still in the preclinical stage. Different types of neurosteroids in the brain share common synthetic pathways, so the dose of individual neurosteroids, the combination of hormone replacement therapies, and even the administration method and frequency may result in different or even completely opposite outcomes (Carroll et al., 2010). A recent study revealed that alterations in the biological clock rhythms interfere with mitochondrial dynamics, thereby affecting neurosteroid production (Witzig et al., 2020). This implies that the normal circadian rhythm can maintain or restore endogenous neurosteroids, but the time of administering exogenous neurosteroids should be tailored to e circadian rhythm. Neurosteroids play an important role in the maintenance of healthy function of the nervous system; however, more research is required to elucidate their sophisticated physiological mechanisms.

Plant extracts

Plants are an important source of new drug discovery, and a considerable number of natural compounds derived from plants have shown significant anti-inflammatory effects both *in vitro* and *in vivo* and verified significant efficacy against AD (Nunes et al., 2020). Huperzine-A is the only plant extract approved by China FDA for the clinical treatment of AD. In addition to inhibiting cholinesterase, Huperzine-A can target AD through various mechanisms such as anti-inflammation, anti-oxidative stress, and regulation of APP metabolism (Zhang et al., 2008). In this section, we focus on several types of common and most representative plant extracts used in AD therapeutic studies.

Quercetin (Que) is a type of flavonoid with neuroprotective function that is widely found in plants. In 3×Tg-AD mice, Que treatment significantly reduced microglial activation around Aβ deposition and IL-1β content in the hippocampus, thereby reducing Aβ burden, protecting neurons, and improving cognitive function in mice (Sabogal-Guáqueta et al., 2015; Vargas-Restrepo et al., 2018). In one study in mice, Que attenuated scopolamine-induced neuroinflammation (reducing TNF-α and IL-6) and mitigated scopolamine-induced cell degeneration and death in hippocampal subregions and the prefrontal cortex, reversing memory impairment (Olayinka et al., 2022). In another study, Que inhibited LPS-induced activation of microglia and astrocytes in adult mice and reduced IL-1β, TNF-α, COX2, and iNOS in the cortex and hippocampus by blocking the TLR4/NF-κB pathway, thereby preventing synaptic dysfunction and improving cognitive function (Khan et al., 2018). Sodium Que-3-rutinoside can reduce neuroinflammation in APP/PS1 mice by promoting Aβ clearance via the upregulation of phagocytic receptors and energy metabolism in microglia (Pan et al., 2019). Another natural flavonoid, luteolin, reduced $A\beta_{1-42}$-induced neuroinflammation and neurodegeneration in rats by inhibiting c-Jun N-terminal kinase (JNK) phosphorylation and astrocyte and microglia activation (Ahmad et al., 2021). In 3×Tg-AD mouse models, luteolin alleviates neuroinflammation by reducing astrocyte hyperactivation through attenuating endoplasmic reticulum (ER) stress (Kou et al., 2022). In human embryonic kidney 293 (HEK293) and SH-SY5Y cells, luteolin is bound to the ER to inhibit NF-κB signaling and BACE1 transcription as an alternative pathway to reduce inflammation and Aβ deposition (Zheng et al., 2015). In an *in vitro* BBB model, luteolin inhibited p38MAPK phosphorylation, attenuated BBB disruption due to $A\beta_{1-40}$ triggering, and promoted inflammation (Zhang et al., 2017b).

A meta-analysis based on six clinical trials showed that curcumin (Cur) significantly improved cognitive function in older adults (Zhu et al., 2019). Cur is a phenolic acid compound with a unique symmetrical molecular structure extracted from the rhizomes of some plants in the Zingiberaceae and Araceae families, and can exert powerful anti-inflammatory activity through a variety of targets. It has hence been widely used in clinical and preclinical studies of AD, showing superior therapeutic promise (Cianciulli et al., 2016; Sarker and Franks, 2018). In 12–16-month-old APPsw Tg2576 mice, oral administration of Cur for 4 months reduced IL-1β and astrocyte activation in the brain and attenuated Aβ burden (Begum et al., 2008). Cur inhibits hippocampal pro-inflammatory cytokine (IFN-γ) production and stimulates anti-inflammatory cytokine (IL-4) production while significantly reducing oxidative stress, improving neuronal viability, and rescuing memory deficits in an AlCl3-induced AD model (ELBini-Dhouib et al., 2021). In addition, Cur significantly downregulated the expression levels of the pro-inflammatory cytokines TNF-α, IL-1β, and macrophage inflammatory protein-1α in p25Tg mice by inhibiting the activation of the p25/cyclin-dependent kinase 5 pathway and significantly improved AD-like pathological changes (phosphorylated Tau and deposition of Aβ) and cognitive impairment (Sundaram et al., 2017). *In vitro* experiments confirmed that Cur inhibits LPS-induced iNOS production in BV-2 cells and primary neurons (Begum et al., 2008). In primary microglia, Cur significantly inhibits Aβ-stimulated pro-inflammatory cytokine production (IL-1β and TNF-α) by suppressing high mobility group protein 1 expression and release as well as TLR4 and receptor for advanced glycation end products (RAGE) expression or by directly blocking extracellular signal-related kinases 1 and 2 and p38 pathways (Shi et al., 2015; He et al., 2020). In addition, Cur can induce reactive microglia to secrete anti-inflammatory factors to mitigate neuroinflammation via calmodulin-dependent protein kinase kinase β activation of the AMP-activated protein kinase signaling pathway, upregulation of triggering receptor expressed on myeloid cells 2 (TREM2) expression, and dose-dependent upregulation of the suppressor of cytokine signaling 1; these actions block the Janus kinase/signal transducer and activator of transcription 3 pathway (Porro et al., 2019; Zhang et al., 2019; Qiao et al., 2020).

Resveratrol is a natural non-flavonoid polyphenolic compound mainly present in grapes and other fruits, which has anti-inflammatory, anti-oxidant, and neuroprotective functions (Rahman et al., 2020). A significant increase in dendritic length and density of pyramidal neurons in the prefrontal cortex and hippocampus was observed after the administration of resveratrol (20 mg/kg, orally) for 60 days in 18-month-old rats (Monserrat Hernández-Hernández et al., 2016). In a retrospective clinical study of mild-to-moderate AD treated with resveratrol, the resveratrol group showed an increase in IL-4 and macrophage-derived chemokines in the cerebrospinal fluid and a decrease in matrix metalloproteinase-9 compared to the placebo group at 52 weeks of treatment, as well as a decrease in the plasma levels of pro-inflammatory factors (TNF-α, IL-12) compared to baseline values. Resveratrol may provide relief from cognitive decline by improving systemic and central inflammation and BBB integrity (Moussa et al., 2017). Similar to Cur, resveratrol can also exert anti-inflammatory effects through multiple targets. In the rat model of AD induced by intrahippocampal injection of $A\beta_{1-40}$, resveratrol significantly attenuated neuroinflammation (reduction of IL-1β and IL-6) in the cortex and hippocampus by activating SIRT1 (Ma et al., 2019b). Likewise, in 3×Tg-AD mice treated with resveratrol for 5 months, SIRT1 was significantly upregulated in the brain, astrocyte activation was inhibited, NF-κB and poly(adenosine diphosphate-ribose) polymerase expression and Aβ burden were reduced, and memory deficits were alleviated (Broderick et al., 2020). In addition to activating SIRT1, resveratrol reduces LPS- and Aβ-induced microglial activation and neuroinflammation by interfering with TLR4 oligomerization and blocking the NF-κB pathway to reduce the secretion of pro-inflammatory factors (TNF-α, IL-1β, IL-6, NO, and MCP-1) while increasing the secretion of anti-inflammatory factors (IL-10 and IL-13) (Capiralla et al., 2012; Zhao et al., 2018). Furthermore, *in vitro*, resveratrol could prevent Aβ-mediated inflammation and oxidative stress in human neural stem cells by activating AMP-activated protein kinase-dependent pathways (Chiang et al., 2018). Recent studies have shown that resveratrol downregulates Aβ-induced caspase-1 and IL-1β expression in BV-2 cells and reduces inflammasome production by modulating the thioredoxin-interacting protein/thioredoxin/NLRP3 pathway (Feng and Zhang, 2019). Interestingly, resveratrol is a natural selective estrogen receptor agonist that has a similar chemical structure to diethylstilbestrol and can exert anti-inflammatory effects by binding to estrogen receptors (Zhao et al., 2018).

In recent years, an increasing number of plant extracts have been found to have significant effects in inhibiting neuroinflammation and improving the pathological changes and conditions of AD (**Additional Table 1**). In addition to natural plant compounds, their synthetic analogs have similar or better therapeutic effects. Plant extracts have multi-targeted anti-inflammatory properties and can be partially supplemented in the daily diet. Thus, plant extracts have become a valuable source of effective therapeutic agents for AD. However, further research is needed to study the techniques for their extraction and purification and to improve their biostability and bioavailability.

Regulation of intestinal flora

The intestinal tract is home to the largest microbial reservoir in the human body, containing several thousand microorganisms. Microbial toxins such as LPS have been successfully used to induce neuroinflammation and AD in animal models, while dysbiosis of intestinal flora balance has also been recognized to be involved in the onset and development of AD (Kim et al., 2021). Transplantation of feces from 10-month-old 5×FAD mice into the intestinal tract of normal C57BL/6 mice activated microglia (upregulation of TNF-α and IL-1β) and increased the expression of p21 as well as suppressed neurogenesis and brain-derived neurotrophic factor expression in the hippocampus, ultimately leading to memory impairment (Kim et al., 2021). By contrast, transplantation of normal intestinal flora has shown positive effects on AD in animal studies. In humans, the comparison of fecal microbiota between normal older subjects and AD patients suggested that the diversity of AD patients' microbiota decreased significantly (Vogt et al., 2017; Zhuang et al., 2018; Haran et al., 2019). Studies have shown that the proportion of *Firmicutes* and other butyrate-producing bacteria decreased, and the proportion of *Bacteroides* increased, and the increase of Bacteroides abundance seemed to be positively correlated with the level of phosphorylated Tau and Aβ burden in the brain (Vogt et al., 2017; Haran et al., 2019).

Supplementation with probiotics and prebiotics can restore the diversity of the intestinal flora, thus reducing intestinal neurotoxic products such as bile acids, phenylalanine, isoleucine, and homocysteine, improving the production of short-chain fatty acids and repairing the intestinal epithelial barrier to improve neuroinflammation in AD (Wang et al., 2019b; de Rijke et al., 2022). In different animal models of AD, almost all the probiotics showed positive therapeutic effects. Among these, *Lactobacillus plantarum*, *Clostridium butyricum*, *Bifidobacterium longum*, and *Lactobacillus lactis subsp. cremoris* significantly attenuated systemic inflammation or neuroinflammation and Aβ burden in experimental mice, while *Lactobacillus plantarum*, *Clostridium butyricum*, and *Bifidobacterium longum* also improved the cognitive function (de Rijke et al., 2022). However, unlike other therapeutic approaches, findings from animal experiments cannot be directly translated into clinical application owing to differences in the microbiome between AD animal models and AD patients. A recent meta-analysis of several clinical trials in AD patients confirmed that supplementation with either single or multiple strains of *Bifidobacterium* and *Lactobacillus* can lead to improved cognitive function (Den et al., 2020). Although supplementation with probiotics is considered beneficial and harmless, many conditions such as genetic background, living environment, and even sex may affect the gut microbiome of patients, and the full therapeutic potential of probiotics needs to be realized through precise analysis.

In addition to restoring bacterial diversity and abundance, clearance of intestinal pro-inflammatory microbes can mitigate neuroinflammation. In contrast to age-matched APP/PS1 mice administered a sterile diet from birth, one study showed that cortical pro-inflammatory cytokines IL-1β, IL-2, IL-5, and IFN-γ were significantly elevated in normal-diet APP/PS1 mice, accompanied by more severe Aβ load (Harach et al., 2017). In another study, APP/PS1 mice treated with a combination of antibiotics (gentamicin, vancomycin, metronidazole, neomycin, ampicillin, kanamycin, mucomycin, and cefoperazone) starting at postnatal 14 days showed significantly reduced brain Aβ deposition and glial cell activation as well as an increased abundance of the Akkermansia genus and Lachnospiraceae family compared to the control group (Minter et al., 2016). Similar results have been observed in humans. In AD patients with *Helicobacter pylori* (*H. pylori*), administration of a 2-year *H. pylori* eradication therapy regimen (omeprazole, clarithromycin, and amoxicillin) significantly improved the Mini-Mental State Examination, Cambridge Cognitive Examination, and Functional Rating Scale for Symptoms in Dementia scores, while cognitive function further decreased in the non-treated and *H. pylori*-negative groups (Kountouras et al., 2009).

Antibiotics can have a positive effect on AD because they improve the balance of intestinal flora by scavenging pro-inflammatory microbes. Moreover, some antibiotics such as doxycycline, minocycline, and rifampicin exhibit properties beyond anti-infection because they inhibit the aggregation of Aβ, phosphorylation of Tau protein, and neuroinflammation *in vitro* (Angelucci et al., 2019). However, there is no more evidence on that specific antibiotics and long-term use of antibiotics have beneficial regulation of the intestinal flora and thus positively affect AD. Moreover, there are many restrictions on the use of antibiotics. Generally, antibiotics are prescribed for the management of acute infections, and the overuse of antibiotics can lead to an increase in drug-resistant bacteria. In addition, long-term antibiotic use can lead to an imbalance in the intestinal flora, which may further aggravate the course of AD (Angelucci et al., 2019). Therefore, it is necessary to identify specific antibiotics that help slow or inhibit progressive neurodegenerative disease and which do not result in secondary infections or dysbiosis of intestinal flora when used at low doses over a long period.

The interaction of gut microbiota with plant extracts has also received significant attention. Oral administration of natural compounds has been shown to regulate the gut microbiota profile; gut microbes can convert natural compounds into bioactive molecules with the potential to improve the inflammatory microenvironment (Wu and Tan, 2019). Sodium oligomannate (GV-971) is an acidic linear oligosaccharide from marine brown algae in dimeric to decameric form (Syed, 2020). In 5×FAD Tg mice, oral administration of sodium oligomannate was shown to regulate intestinal ecological dysregulation and inhibit the production of amino acids such as phenylalanine and isoleucine. This prevented the differentiation of CD4 T cells to T-helper type 1 cell, alleviating the infiltration of T-helper type 1 cell into the brain and facilitating microglial activation, and thereby alleviating neuroinflammation and improving cognitive impairment (Wang et al., 2019b). In another study, sodium oligomannate inhibited the formation of Aβ fibrils by binding to multiple sub-regions of Aβ after penetrating the BBB mediated by glucose transporter 1, and decomposed the pre-formed fibrils into non-toxic monomers, reducing the neurotoxicity of Aβ (Wang et al., 2019b; Syed, 2020). Sodium oligomannate has completed a phase III clinical trial (NCT02293915) in China and was first approved in China in November 2019 for the treatment of mild-to-moderate AD.

Macromolecules

Monoclonal antibodies targeting Aβ and Tau to directly relieve the pathological burden of AD have been a hot topic in current studies. The phase III Clarity AD trial of Lecanemab (BAN2401), a monoclonal antibody targeting Aβ, was reported to have reached its primary endpoint and is the second Aβ monoclonal antibody approved by the U.S. FDA. However, most monoclonal antibodies are still in the preclinical stage, and the approval of the first Aβ monoclonal antibody Aducanumab by the U.S. FDA is accompanied by much controversy because of its inadequate evidence of efficacy and adverse effects such as Aβ-related imaging abnormalities (e.g., edema and microhemorrhage) (Knopman et al., 2021). The over-activation of microglia and astrocytes and the subsequently sustained secretion of inflammatory factors such as TNF-α, IL-1β, and IL-6 are important factors contributing to the accelerated progression of AD. Therefore, monoclonal antibodies that target inflammatory factors or inflammatory pathways to interrupt the vicious cycle between inflammation and AD pathology and thus slow down or even reverse the progression of AD hold great therapeutic promise.

Targeting IL-1β to treat AD was proposed as early as 2010 (Mitroulis et al., 2010) but unfortunately there are no dedicated clinical or animal studies. More recently, a large-scale retrospective case-control study of electronic health records of 56 million adult patients suggested that the use of one TNF-α monoclonal antibody (etanercept, adalimumab, or infliximab) in patients with inflammatory diseases (rheumatoid arthritis, psoriasis, ankylosing spondylitis, inflammatory bowel disease) significantly reduced the risk of AD, with a greater benefit in younger patients. However, there was no direct evidence that the reduction in AD risk by TNF-α monoclonal antibodies was directly associated with attenuated neuroinflammation (Zhou et al., 2020b). In a streptozotocin-established AD rat model, tocilizumab treatment for 3 weeks (1.5 mg/kg, ICV injection) significantly reduced IL-6 levels in the cortex, alleviated Aβ burden, and improved cognitive impairment (Elcioğlu et al., 2016). In another study, injection of IL-17a monoclonal antibody via the pre-placed ICV cannula during hepatic lobectomy also attenuated neuroinflammation and transcriptional levels of APP and Aβ in the hippocampus and improved spatial working memory in postoperative mice (Tian et al., 2015).

In addition to inflammatory factors, key nodes of inflammatory pathways can be considered therapeutic targets. The coagulation factor fibrinogen is an important activator of neuroinflammation, linking BBB destruction with CNS innate immunity. The coagulation factors fibrinogen and fibrin are important activators of neuroinflammation, linking BBB destruction with central innate immunity. Based on this, the first fibrin immunotherapy was developed, targeting the fibrin epitope γ377-395 with the highly selective monoclonal antibody 5B8 without affecting coagulation (Ryu et al., 2018). In 5×FAD mice, 5B8 reduced Aβ-induced microglial activation and neurodegeneration by inhibiting fibronectin/CD11b signaling and expression of the *Tyrobp*-related gene network (Ryu et al., 2018). Recently, monoclonal antibodies targeting such as AB-T1 targeting membrane-bound and soluble TREM2 was developed by researchers (Fassler et al., 2021). Ab-T1 activated membrane-bound TREM2-mediated acute inflammatory responses of microglia to clear Aβ and inhibited soluble TREM2-induced chronic neuroinflammation. In animal studies, Ab-T1 administered once a week prevented and retarded the development of cognitive impairment in young 5×FAD mice with intact cognition and no plaques, while Ab-T1 administered to aged 5×FAD mice twice a month was also effective in mitigating cognitive impairment (Fassler et al., 2021).

Monoclonal antibodies, as typical representatives of large molecule drugs, have significant potential to treat AD. However, the inflammatory background of AD is intricate and complex, so targeting a single site may not achieve the desired therapeutic effect. Future studies could consider them as part of the anti-inflammatory cocktail therapy for AD by targeting specific inflammatory pathways or inflammatory factors to enhance the therapeutic effect.

Gene therapy

Microglia play a core role in neuroinflammation, and the regulation of target gene transcription and post-transcriptional translation can modulate microglial function or control the secretion of inflammatory mediators, thereby reducing neuroinflammation. *Trem2* plays an important role in regulating microglial function, and it is generally believed that upregulation of *Trem2* expression tends to show a protective effect against AD. In one study, targeted delivery of *p-Trem2* to microglia enabled efficient gene transfection, upregulated Trem2 expression levels, and activated anti-inflammatory function of microglia to reshape the inflammatory microenvironment and enhance Aβ clearance, thereby improving cognitive performance in APP/PS1 mice (Wang et al., 2022b). Interestingly, a recent study confirmed that short-term administration of *Trem2* antisense oligonucleotides to temporarily downregulate TREM2 expression is beneficial in late-stage AD. Moreover, a single ICV injection of *Trem2*-ASOs effectively reduced *TREM2* mRNA levels in the brains of APP/PS1 mice. Inflammatory gene expression increased dramatically at 1 week after *TREM2* mRNA reduction to prompt plaque clearance, and decreased at 1 month of TREM2 reduction which meant that the reduction of Aβ plaque lessened the reactivity of microglia (Schoch et al., 2021). This suggests the complexity of *Trem2* in regulating the function of disease-associated microglia and the necessity to regulate *Trem2* positively or negatively in the particular stage of AD to ultimately reduce neuroinflammation.

CD33 is another vital target for the regulation of microglia. ICV injection of artificial microRNA targeting CD33 (miRCD33) in APP/PS1 mice to reduce CD33 mRNA in brain extracts resulted in the downregulation of pro-inflammatory genes (encoding TLR4 and IL-1β) and reduction in TNF-α, soluble Aβ, and Aβ deposition, especially after early (2 months) and long-term intervention (Griciuc et al., 2020). Additionally, dozens of miRNAs were identified to mediate neuroinflammation in AD (Saika et al., 2017). miRNA-34a mediates TREM2 downregulation in microglia, whereas anti-miRNA-34a (AM-34a) reverses this outcome (Zhao et al., 2013). In one study, miRNA-485-3p induced microglia to secrete pro-inflammatory factors (IL-1β and TNF-α) and exacerbated Tau phosphorylation, Aβ burden, and synaptic damage, while miR-485-3p ASO ameliorated these changes (Koh et al., 2021). Importantly, for different nerve cells, the same miRNAs may act in a completely opposite regulatory direction. Inhibition of miR-146a in $A\beta_{1-42}$-treated rat pheochromocytoma (PC12) cells and rat primary cortical neurons attenuated apoptosis and secretion of inflammatory factors (TNF-α, IL-1β, IL-6, IL-17) and enhanced neuronal viability (Ma et al., 2021). However, regulation of miR-146a in microglia resulted in a different outcome. After injection of microglia-specific miR-146a into the hippocampus of 10-month-old APP/PS1 Tg mice by using a stereotactic technique, microglia-specific miR-146a showed obvious microglia targeting, reduced neuroinflammation, and improved clinical symptoms and pathological changes (Liang et al., 2021). The diversity of miRNAs associated with AD is abundant; therefore, different regulations of targeted miRNAs in different cells, lesion sites, and 19 different phases of AD are required to achieve the ultimate shared purpose of improving inflammation.

In addition to miRNAs, other non-coding RNAs such as long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have been found to participate in the process of AD. Some lncRNAs and circRNAs can mediate neuroinflammation by regulating miRNAs (Yang et al., 2019; Zhou et al., 2020a; Li et al., 2022b). Regulation of miRNA expression through lncRNAs or circRNAs can indirectly alleviate neuroinflammation. Non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lnc-MALAT1) can also inhibit neuronal apoptosis, promote neurite growth, reduce IL-6 and TNF-α levels and elevate

IL-10 levels by reversely regulating miR-125b expression in $A\beta_{1-42}$-treated PC12 cells and rat cortical neurons (Ma et al., 2019a). Apart from the above non-coding RNAs, small interfering RNA (siRNA) is also frequently used for the treatment of AD. siRNA is a double-stranded RNA that is mostly artificially synthesized, and most of the siRNAs currently used to treat AD are designed to decrease BACE1 expression, thereby reducing $A\beta_{1-42}$ production. Recently, ROCK2-siRNA targeting microglial Rho kinase was designed to specifically reduce Aβ and LPS-induced IL-1β production by inhibiting NLRP3/caspase-1 without affecting TNF-α (Liu et al., 2022).

Dozens of agents based on anti-inflammatory treatments for AD are currently in clinical trials; unfortunately, none of them are gene therapies (**Figure 2**). Gene therapy for AD is currently in its infancy and requires large-scale studies in humans to identify key target genes for specific disease phases, specific brain regions, and different cells to enhance the efficacy and safety of the therapeutics.

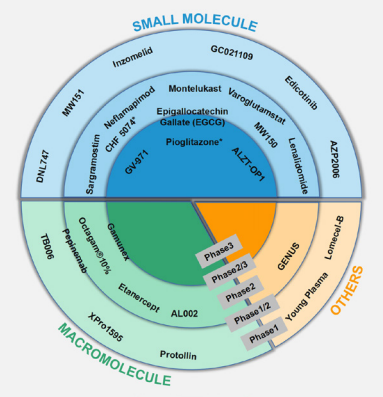

Figure 2 | **Agents currently used in clinical trials for the anti-inflammatory-based treatment of Alzheimer's disease.**
*indicates mild cognitive impairment. Created with PowerPoint.

Application of Biomaterials in the Anti-Inflammatory Therapy of Alzheimer's Disease

Animal studies have shown that after oral administration of NSAIDs, drug concentrations in the brain can reach only up to one-tenth of the plasma (Eriksen et al., 2003). This is mainly attributed to the presence of the BBB. The BBB is primarily composed of vascular endothelial cells, pericytes, and astrocytes, which strictly control the exchange of substances between the brain and the periphery and prevent peripheral toxic substances from entering the CNS, while blocking almost all small and large molecule drugs and genetic agents from accessing the CNS. However, it was mentioned above that increased permeability of the BBB can lead to the penetration of peripheral inflammatory factors and toxic products into the CNS, thereby increasing neuroinflammation. However, in this case, the disruption of BBB integrity does not actually improve drug concentration in the brain as expected due to the impaired function of endothelial cells and perivascular accumulation of toxic products (Sweeney et al., 2018). Besides the BBB, the stability and bioavailability of the drug in the body are also key factors affecting treatment, especially for lipid-soluble drugs such as plant extracts (Leclerc et al., 2021). To overcome these disadvantages, nanoparticles should be considered.

Lipid-based nanoparticles

Liposomes

Liposomes are spherical organic nanoparticles formed by lipid bilayers (most often, phospholipid) with diameters ranging from 25 nm to 5000 nm. The external lipid layer is similar in structure to the phospholipid bilayer of cell membranes and is loaded with lipophilic drugs, while the hydrophilic core can be loaded with water-soluble drugs (**Figure 3A**; Hernandez and Shukla, 2022). In terms of liposomes, their constituents may have beneficial effects on AD. Phosphatidic acid, a common major component of liposomes, can inherently target Aβ and improve Aβ burden and memory impairment, as shown in an AD mouse model (Balducci et al., 2014). Moreover, phosphatidylserine/phosphatidylcholine liposomes prepared from phosphatidylserine and phosphatidylcholine in the ratio of 3:7 significantly inhibited Aβ-induced activation of microglia, as exhibited by reduced production of TNF-α and ROS (Hashioka et al., 2007). Phosphatidylserine liposomes loaded with metformin significantly reduced the levels of cytokines IL-1β, TNF-α, and TGF-β in hippocampal tissue and improved learning and memory of the streptozotocin-induced AD rat model (Saffari et al., 2020).

As a drug-delivery carrier with high biocompatibility and biodegradability, the special design of liposomes can significantly improve the drug entrapment rate and stability, and thus deliver drugs to the CNS more efficiently. The addition of stearic acid to the bilayer of the liposome can improve the stability of particles, increase the drug entrapment efficiency and prolong the duration of drug release (Kuo et al., 2021). The addition of cardiolipin to liposomes composed of soy phospholipids, cholesterol, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanol-amine-N-[methoxy (polyethylene glycol)-2000] (DSPE-PEG(2000)) enhanced the retention of Cur. Cur retention of liposomes composed of 1, 2D-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), cholesterol, DSPE-PEG2000, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (DSPE-PEG(2000)-CA) was enhanced by the addition of cardiolipin, and penetration of the BBB was significantly improved by the electrostatic adsorption and recognition of N-acetylglucosamine to target vascular endothelial cells by grafted wheat germ agglutinin (Kuo and Lin, 2015). Additionally, egg phosphatidylcholine, cholesterol, DSPE-PEG2000, and osthole (Ost) were prepared as liposome Ost-Lip in the ratio of 100:40:3.8:17.3 molar by the thin-film hydration method and was modified to produce Tf-Ost-Lip by transferrin (Tf). There was no clear difference in cytotoxicity between Ost-Lip and Tf-Ost-Lip, but Tf-Ost-Lip exhibited higher central targeting and penetration efficiency of the BBB and significantly improved hippocampal inflammation (downregulation of IL-1β, IL-6, and TNF-α), Aβ burden, and cognitive function in APP model mice (**Figure 3B** and **C**; Kong et al., 2020). Similarly, a liposome composed of 1,2-distearoyl-sn-glycero-3-phosphatidylcholine, DSPE-PEG2000, DSPE-PEG2000-COOH, and cholesterol exhibited excellent encapsulation ability and stable release rate of α-mangostin and showed superior BBB penetration after Tf modification (Chen et al., 2016).

In addition to Tf, many surface modification ligands increase the BBB penetration ability of nanocarriers. ApoE-modified phosphatidic acid liposomes carrying Que and rosmarinic acid targeted the BBB and Aβ via ApoE and palmitic acid, respectively, thereby increasing the concentration of the loaded drugs at the lesion site and reducing neuroinflammation and neuroapoptosis in an AD rat model (Kuo et al., 2020). Angiopep-2, a short 19-amino acid peptide targeting low-density lipoprotein receptor-associated BBB proteins, modified egg yolk phosphatidylcholine liposome loading icariin and tanshinone IIA showed stronger brain targeting ability than unmodified liposomes; its action improved neuroinflammation, neuroapoptosis, and cognitive function in APP/PS1 mice (Wang et al., 2022a). Recently, dual or more complex surface modifications were designed to increase the efficiency of liposomes penetrating the BBB. Compared to Pen- (cell-penetrating peptide-) or Tf-modified liposomes, liposomes co-modified with Pen and Tf were significantly more efficient in delivering ApoE2 to the CNS (Dos Santos Tramontin et al., 2020). Co-loading of various neuroprotective agents such as Cur, Que, epigallocatechin gallate, and RA into phosphatidylcholine-liposomes, with modification by glutathione and ApoE, can enhance their neuroinflammatory and neuronal protective effects via glutathione and ApoE targeting to the BBB and ApoE and phosphatidylcholine targeting to Aβ, and was validated in an *in vitro* BBB model and human neuroepithelial (SK-N-MC) cells (Kuo et al., 2021).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are typically characterized by the lipid core, which is solid at room temperature, and it has the surfactant shell, which maintains its stability (Scioli Montoto et al., 2020). Nanoparticles composed of a pure solid core are called SLN, while those developed by mixing a small amount of liquid lipid into a solid core to induce matrix structural rearrangement are called nanostructured lipid carriers (NLCs). In general, NLCs are considered as an upgraded version of SLNs because although they have a similar structure, NLCs show a higher drug-loading capacity and long-term physicochemical stability (**Figure 4A**; Pinheiro et al., 2020; Scioli Montoto et al., 2020).

SLNs have an excellent drug encapsulation rate and biostability. In a study that used the solid lipid (cetyl palmitate) to produce an SLN and blended it with liquid lipid (miglyol-812) to form an NLC, the entrapment rate for Que reached 81 ± 12% and 97 ± 10%, for the SLN and NLC respectively (Pinheiro et al., 2020). The SLN, also prepared from cetyl palmitate, exhibited an encapsulation rate between 75% and 100% for different concentration gradients of resveratrol and grape extract, and the cargo was released in a controlled manner that effectively inhibited Aβ fibrosis (Loureiro et al., 2017). Glyceryl behenate-SLN-loaded Cur increased its bioavailability by 32–155 fold and improved cognitive dysfunction in a dose-dependent manner in $AlCl_3$-induced AD mice (Kakkar and Kaur, 2011). Moreover, even the lowest dose of SLN-loaded Cur (1.0 mg/kg) can significantly reduce oxidative stress in neurons and promote the normalization of brain microstructure compared to free Cur (Kakkar and Kaur, 2011). Glycerin monostearate-SLN-loaded erythropoietin and piperine significantly improved cognitive function and reduced oxidative stress and Aβ burden in the hippocampus in Aβ-induced AD rats compared to controls at the same dose (Yusuf et al., 2013; Dara et al., 2019). Besides many candidates, SLN can significantly improve the pharmacokinetic and therapeutic efficacy of drugs currently approved in the clinical treatment of AD. Stearic acid-SLN provided a minimum encapsulation rate of 88% for lipoyl-memantine with a 1:2.5 drug:lipid ratio and showed excellent biosafety and biostability (Laserra et al., 2015). Glyceryl sorbate-SLN achieved a minimum drug encapsulation rate of 83.42 ± 0.63% for galantamine and provided approximately twice the bioavailability of free galantamine, with significant recovery in cognitively deficient rats, as assessed *in vivo* (Misra et al., 2016). Compared to the release of free galantamine, which was nearly 80.96% in 1 hour, the release of SLN-galantamine was > 90% during 24 hours in a controlled manner *in vitro* (Misra et al., 2016). Tocopherol succinate-SLN was also effective in encapsulating rivastigmine and exhibited sustained and controlled release in an *in vitro* assay (Malekpour-Galogahi et al., 2018).

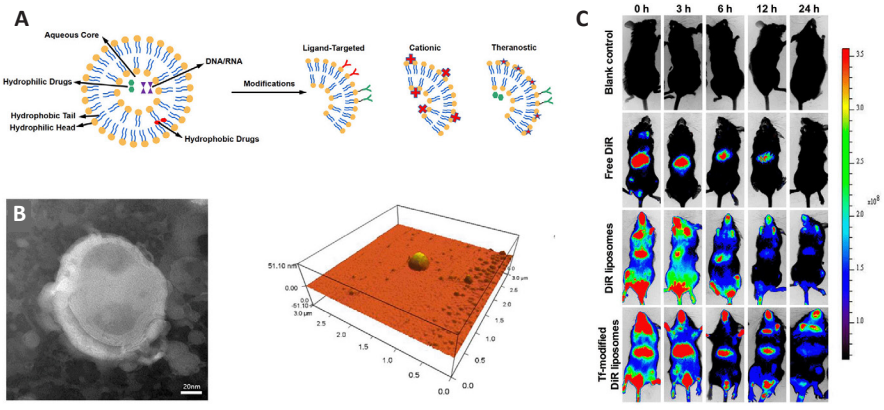

Figure 3 | The basic structure of liposomes and their role in permeating the blood-brain barrier.
(A) Basic structure and modification of liposomes. Ligand-targeted liposomes: Ligand-like antibodies or peptides on the surface of liposomes bind to specific receptors on the BBB to promote endocytosis. Cationic liposomes: Positive charges on liposomes interact with polyanions on the BBB, thus promoting endocytosis. Therapeutic diagnostic liposomes: multifunctional liposomes with therapeutic and diagnostic capabilities such as carrying drugs and noninvasive contrast agents. Reprinted from Hernandez and Shukla (2022). (B) Transmission electron microscopy image of Tf-Ost-Lip and three-dimensional structure of the atomic force microscopy image. Tf-Ost-Lip was spherical with a smooth surface and measured approximately 100 nm in diameter. Reprinted from Kong et al. (2020). (C) Images of the distribution of different liposomes in APP/PS1 mice after intravenous injection (n = 3). Intense fluorescent signals were observed in the brain after administration of the DiR liposome and Tf-modified DiR liposome, and the signal of the Tf-modified DiR liposome was maintained for up to 24 hours. Adapted from Kong et al. (2020). DIR: 1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide; Ost: osthole; Tf: transferrin.

To exploit the drug delivery potential of SLN, a five-level central composite design was used to analyze mathematical models of the relationship between the independent variables (surfactant concentration and drug/lipid ratio) and the dependent variables (particle size, drug encapsulation efficiency, and loading efficiency) to obtain the optimal formulation of SLN (Malekpour-Galogahi et al., 2018). Additionally, appropriate surface modifications can enhance the ability of SLN to deliver drugs to the brain. After surface modification with the OX26 monoclonal antibody, which specifically targets the Tf receptor on the BBB, the BBB penetration efficiency of cetyl palmitate-SLN was increased 2-fold (Loureiro et al., 2017). In an *in vitro* experiment, NLC-rabies virus glycoprotein (RVG) Que and SLN-RVG Que modified with RVG29 peptide—a 29-amino acid fragment derived from rabies virus glycoprotein that targets nicotinic acetylcholine receptors on BBB and neurons—showed significantly higher efficiency in penetrating the BBB (**Figure 4B–D**) than unmodified ones and markedly inhibited the aggregation of Aβ (Pinheiro et al., 2020).

Biological cell membrane

The accumulation of synthetic nanoparticles and their metabolites may trigger immune and inflammatory responses, induce oxidative stress, and thus cause unintended side effects on the brain (Guo et al., 2017). Therefore, natural lipid nanovesicles derived from biological cell membranes such as exosomes are very promising drug delivery vehicles owing to their unique advantages of low toxicity, non-immunogenicity, biodegradability, and biocompatibility.

Exosomes are intraluminal vesicles with a lipid bilayer formed by the inward budding of the restrictive membrane of the multivesicular endosome, usually 50–150 nm in diameter. Many types of cells can secrete exosomes under normal or pathological conditions. Over the past decade, exosomes in the brain have been proposed to play an important role in promoting inflammation, Aβ deposition, and the spread of abnormal phosphorylation of tau in AD (Dinkins et al., 2017). Additionally, exosomes can be applied as therapeutic agents and drug delivery vehicles in AD. Exosomes derived from stem cells are very promising candidates for the treatment of AD, and those obtained after pretreatment with inflammatory factors or hypoxia appear to have better therapeutic potential (Cui et al., 2018; Losurdo et al., 2020). Exosomes isolated from healthy donor-derived bone marrow mesenchymal stem cells inhibited TNF-α and IFN-γ stimulation of primary microglia and polarized them toward the anti-inflammatory phenotype *in vitro* (Losurdo et al., 2020). After intranasal administration, extracellular vesicles derived from mesenchymal stem cells reduced the activation of microglia and increased the density of neuronal synapses in the brains of 3×Tg mice (Losurdo et al., 2020). Systemic administration of exosomes isolated from both human umbilical cord mesenchymal stem cells and hypoxia-pretreated mesenchymal stem cell stromal cells showed attractive therapeutic potential, such as inhibition of microglia and astrocytes activation, downregulation of pro-inflammatory factors and upregulation of anti-inflammatory factors, reduction of Aβ deposition, and improvement of cognitive function (Cui et al., 2018; Ding et al., 2018). Unfortunately, the therapeutic mechanism of exosomes is currently unclear and may be partially attributed to the fact that they still maintain some of the inherent neuroprotective functions of the parental cells. Given their similar structure to other cell vesicles and liposomes, exosomes can also be used as drug delivery carriers for AD. Exosomes derived from the mouse leukemic monocyte macrophage cell line (RAW 264.7) and rat whole blood cells loading with Cur and Que, respectively, both showed much higher brain aggregation than free drug (**Figure 5A–C**) and attenuated tau hyperphosphorylation in the AD mice model, resulting in neuroprotective and cognitive improvement effects (Wang et al., 2019a; Qi et al., 2020). Thus, exosomes can also exert synergistic neuroprotective effects with the loaded agents (Qi et al., 2020). Exosomes can likewise be target-modified to enhance brain-targeting capability. One study fused RVG peptide to Lamp2b, a membrane protein expressed in dendritic cells, by plasmid transfection to achieve functional modification, and then obtained exosomes for delivery of *BACE1*-siRNA. Results of animal experiments demonstrated that the level of *BACE1* mRNA was significantly reduced in the modified group (61 ± 13%), and the levels of BACE1 and $A\beta_{1-42}$ protein decreased by 62% and 55%, respectively (Alvarez-Erviti et al., 2011). Given the anti-inflammatory effects of a variety of plants, exosomes derived from plant cells have received increasing attention in recent years apart from animal cell exosomes. Vesicle-like nanoparticles extracted from ginger, garlic chive, and shiitake mushroom have been identified to inhibit the activity of NLRP3 inflammasome and improve systemic chronic inflammation in experimental animals (Liu et al., 2021a). Natural exosomes derived from anti-inflammatory plants may become new options that are beneficial for AD.

Compared to the passive collection of extracellular vesicles, the active disruption of cells to obtain cell-derived nanovesicles has the advantages of more yield and less cost. The celecoxib (CB) encapsulation efficiency of erythrocyte membrane vesicles (CB-RBCM) prepared by extrusion was 90.0 ± 0.3%, which was like the control CB-phospholipid-liposome (CB-PSPD-LP) of 98.4 ± 0.8% (Guo et al., 2017). Both CB-RBCM and CB-PSPD-LP exhibited higher brain transport efficiency than free CB and avoided the neurotoxicity of a high concentration of abruptly released celecoxib through a controlled and slow-release pattern (Guo et al., 2017). Moreover, CB-RBCM showed higher brain distribution and neuronal uptake of CB after intranasal administration in APP/PS1 Tg mice compared to CB-PSPD-LP and exhibited better neuroprotection and memory recovery (Guo et al., 2017). Although erythrocytes are the most abundant and accessible cells in biological systems, nanocarriers derived from erythrocyte membranes need to conform to strict blood type identity. Therefore, one study exploited the innate chemotactic ability of macrophages to localize the inflammatory environment to prepare macrophage membrane-encapsulated glycerol monostearate SLN-genistein (GS) biomimetic nanosystem MASLN-GS by extrusion and then postinsertionally modified by RVG29 and TPP (triphenylphosphine cation, targeting the negative potential of the mitochondrial membrane) to form RVG-MASLN-GS, TPP-MASLNs-GS, and RVG/TPP-MASLN-GS, respectively (**Figure 5D** and **E**; Han et al., 2021). *In vitro*, RVG/TPP-MASLNs more readily crossed the BBB and were internalized into the mitochondria of HT22 cells. Furthermore, in APP/PS1 Tg mice, RVG/TPP-MASLNs-GS ameliorated cognitive deficits more strongly than other agents and significantly attenuated Aβ deposition and oxidative stress in the brain, while preventing abnormal activation of glial cells and neuroinflammation (Han et al., 2021). Recently, studies have used melanoma cells loaded with TNF-α ASO and then induced apoptosis to produce apoptotic vesicles (Wang et al., 2021). TNF-α ASO-containing apoptotic vesicles still retain the property of brain metastasis derived from melanoma cells and efficiently deliver TNF-α ASO into the CNS, reducing brain TNF-α levels and microglia and astrocyte activation (reducing IFN-γ, IL-1β, and IL-6 levels) in male C57BL/6J mice (Wang et al., 2021).

Polymer nanoparticles

Polymeric nanoparticles can be defined as colloidal systems including nanocapsules or nanospheres (NS), micelles, dendrimers, and nanogels (NGs), consisting mainly of natural polymers such as peptides, polysaccharides, and polyhydroxyalkanoates and synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(amido-amine) (PAMAM), poly(ethylene glycol)-poly(lactic acid), and poly(ethylene glycol)-poly(caprolactone), typically in the diameter range of 100–500 nm (Furtado et al., 2018; Lu et al., 2021). Polymeric nanoparticles offer superior drug encapsulation efficiency, greater stability of the packaged active substances, higher intracellular uptake, excellent biocompatibility with tissues and cells, and biodegradability when prepared from low-toxicity polymers. Importantly, polymeric nanoparticles are easily modified and can be designed to deliver drugs to targeted sites of interest, thereby improving therapeutic efficacy and minimizing side effects (Lu et al., 2011).

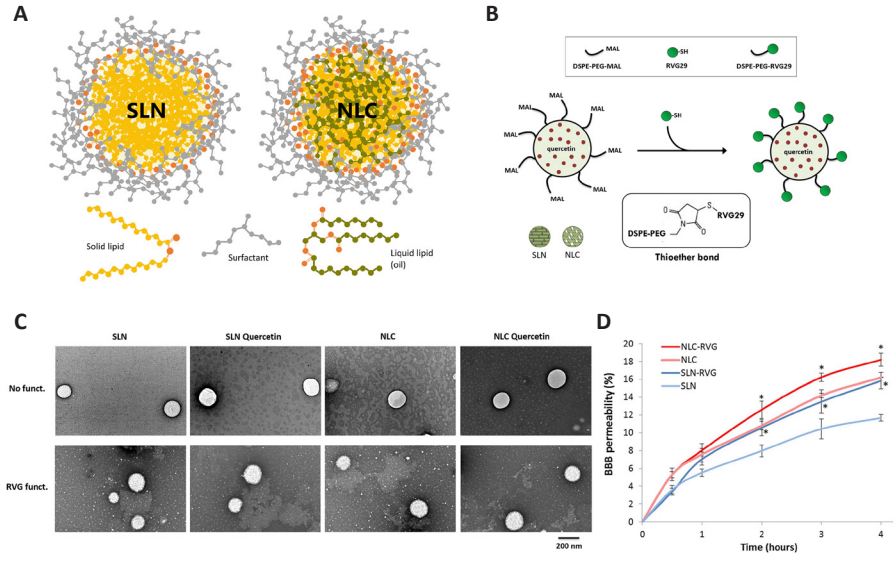

Figure 4 | Basic structure and capacity of SLN for BBB penetration.

(A) Schematic diagram of SLN and NLC. A small amount of liquid lipid was added to the solid core of NLC. Reprinted from Scioli Montoto et al. (2020). (B) Schematic diagram of Que-loaded SLN and NLC functionalized with RVG29 peptide. MAL can react with the thiol group (-SH) to form a thioether bond. (C) TEM images of non-functionalized and RVG29-functionalized NPs showed a size of approximately 200 nm, spherical shape, and homogeneous morphology. Furthermore, the encapsulation of Que and functionalization of the RVG29 peptide did not seem to change the size, morphology, and stability of the NPs. (D) Permeability of RVG29 peptide-functionalized NPs on hCMEC/D3 monolayers. The permeability of RVG29-NPs was significantly increased (1.5-fold higher) compared to that of non-functionalized nanoparticles. Data were represented as the mean ± SD (n = 3). *P < 0.05, *vs.* respective non-functionalized nanoparticles. B–D were reprinted with permission from Pinheiro et al. (2020). Copyright 2020, Springer Science Business Media, LLC, part of Springer Nature. DSPE-PEG: 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)]; MAL: maleimide group; NLC: nanostructured lipid carrier; NP: nanoparticle; Que: quercetin; RVG: rabies virus glycoprotein; SLN: solid lipid nanoparticle.

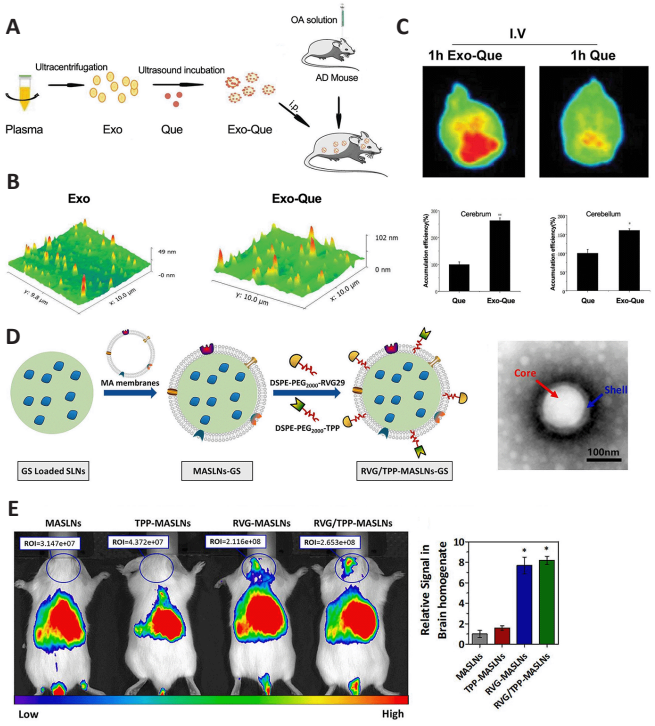

Figure 5 | The basic structure of biological cell membrane-based nanocarriers and penetration of the blood-brain barrier.

(A) Que-loaded exosomes were harvested by ultracentrifugation and subsequent ultrasonication and treated for the AD mouse model via tail vein injection. (B) The particle size of Exo and Exo-Que under an atomic force microscope. The diameters of Exo and Exo-Que are mainly distributed at 125 and 150 nm. (C) Brain-targeting effects of Que and Exo-Que in mice via intravenous (I.V.) injection. Exo-Que significantly enhanced the accumulation of Que in the brain. *P < 0.05, **P < 0.01, *vs.* Que. A–C were reprinted from Qi et al. (2020). (D) Schematic preparation and transmission electron microscopy of RVG/TPP-MASLNs-GS. Transmission electron microscopy verified the macrophage membrane-encapsulated SLNs. (E) Brain targeting ability of RVG/TPP-MASLNs-GS *in vivo*. A high accumulation of DIR-labeled RVG-MASLNs was detected in the brain at 1-hour post-injection. Data are presented as means ± SD (n = 3). *P < 0.05, *vs.* MASLNs. D and E were reprinted from Han et al. (2021). AD: Alzheimer's disease; DSPE-PEG2000: 1,2-dipalmitoyl-sn-glycero-3-phosphoethanol-amine-N-[methoxy (polyethylene glycol)-2000]; Exo: exosome; GS: genistein; i.p.: intraperitoneal injection; MASLNs: macrophage membrane-coated solid lipid nanoparticles; OA: okadaic acid; Que: quercetin; RVG: rabies virus glycoprotein; TPP: triphenylphosphine.

Nanocapsules/NS

Nanocapsules are composed of the oil or aqueous core in which the drug is often dissolved, and are surrounded by polymer shells, which control the release profile of the drug from the core. Nanospheres are based on the continuous polymer networks in which the drug can be retained inside or adsorbed onto the surface (**Figure 6A**). The most common synthetic raw material for nanocapsules and NS is PLGA, while the most common natural material is chitosan (CS) (Zielińska et al., 2020).

Researchers developed a brain delivery formulation of dextro-ibuprofen (DXI) based on PLGA NS and DXI-PLGA-PEG NS, which comprise PLGA surrounded by PEG chains (Sánchez-López et al., 2017). The drug encapsulation efficiency of NS with different formula parameters was greater than 80%. DXI-PLGA-PEG NS significantly reduced the activation of microglia and astrocytes in the hippocampus, thereby reducing Aβ deposition. In addition, DXI-PLGA-PEG NS were more effective than free drugs in mitigating memory impairment (Sánchez-López et al., 2017). PLGA-based nanoparticles can improve drug release patterns, widen administration intervals, and reduce the dosage. PLGA-loaded Cur was more efficiently absorbed by human neuroblastoma cell line (SK-N-SH) and had better neuroprotective effects than the equivalent dose of free Cur (Doggui et al., 2012). Surface modifications are necessary to improve the efficiency of nanocarriers to penetrate BBB. PLGA NPs loading Cur and S1 peptide that can bind to the cleavage site of BACE1 on APP, exhibited enhanced BBB penetration efficiency and increased brain accumulation after modification with cyclic CRTIGPSVC peptide, an iron-mimic peptide with the ability to target the Tf receptor (**Figure 6B** and **C**), and more effectively reduced IL-6 and TNF-α levels; inhibited microglia and astrocyte activation; and improved Aβ load and memory deficits in AD mice (Huang et al., 2017). Nanocapsules or NS can also be designed to release drugs at targeted lesions. An ROS-responsive (polyol-ox-PLGA) core loaded with rapamycin (**Figure 6D**) and modified with KLVFF peptide (targeting Aβ) and DAG peptide (targeting connective tissue growth factor to specifically localize to endothelial cells and reactive astrocytes of neurovascular units in lesions) was prepared to form R@(ox-PLGA)-KcD. During the penetration of the BBB, R@(ox-PLGA)-KcD can evade the lysosomal pathway through the acid response of DAG and cleave to R@(ox-PLGA)-K to enter the cerebral parenchyma (Lei et al., 2021). In AD mice, R@(ox-PLGA)-KcD exhibited significant brain targeting. Both at low and high doses, R@(ox-PLGA)-KcD-administered mice showed significantly better retention of spatial learning and memory, improvement of the hippocampal inflammatory microenvironment (**Figure 6E** and **F**), and reduction of Aβ plaque and tau protein burden than free rapamycin treated group (Lei et al., 2021).

CS is a natural biopolymer that possesses the properties of biodegradability, high biocompatibility, non-toxicity, and non-allergenicity. Many studies have used CS to assemble into nanocapsules or NS and cross the BBB by adsorption-mediated transcytosis with its cationic nature. At one-sixth of the recommended therapeutic dose of berberine, CS berberine nanoparticles significantly improved learning and memory functions and reduced oxidative stress and Aβ toxicity in the rat hippocampus (Saleh et al., 2021). There is a study to conjugate positively charged CS and negatively charged bovine serum albumin to form CS-bovine serum albumin NPs. In an *in vitro* BBB model, the permeation efficiency of Cur loaded with CS-bovine serum albumin NPs was improved, as demonstrated by an increase in the penetration efficiency to 37.7% at 1 hour, 45.6% at 2 hours, and 60.2% at 3 hours, compared to 12.3%, 20.3%, and 29.8% for free Cur, respectively (Yang et al., 2018b). Moreover, Cur-loaded CS-bovine serum albumin NPs further inhibited the release of pro-inflammatory factors of disease-associated microglia and enhanced microglia phagocytosis of $A\beta_{42}$ compared with free Cur (Yang et al., 2018b). Furthermore, CS can be hydrolyzed into neuroprotective oligosaccharides by lysosomes *in vivo*, which can exert beneficial effects on AD such as anti-inflammation and anti-apoptosis (Zhang et al., 2021). CS also has the property of mucoadhesion and is particularly suitable to achieve drug penetration through mucous membranes. Drugs such as Cur, piperine, and 17β-estradiol loaded in the CS carrier and administered intranasally have also been shown to be superior to free drugs in terms of accumulation in the brain and improvement of AD condition (Manek et al., 2020). In addition to being the

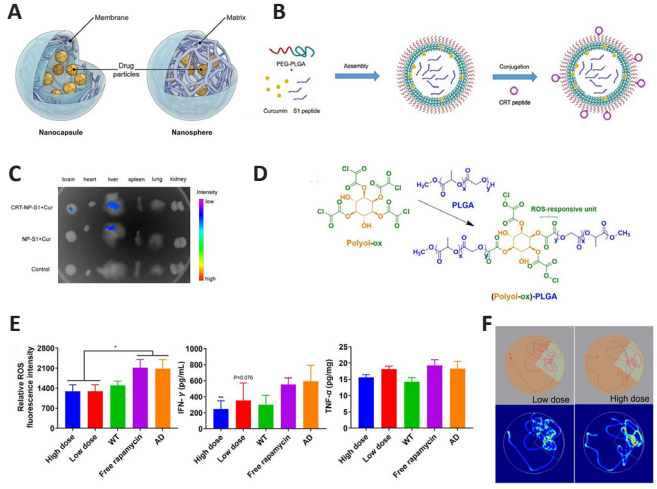

Figure 6 | **The basic structure of the nanocapsules or NS and their potential as nanocarriers to cross the BBB.**
(A) Schematic diagram of the basic structures of nanocapsules and NS (Furtado et al., 2018). Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission. (B) Schematic diagram of PLGA nanoparticle fabrication. PLGA NPs were prepared by self-assembling PEG-PLGA with curcumin and S1 peptide and conjugated with CRT peptide. (C) Fluorescence intensity of various mice organs at 24 hours after administration of PLGA NPs. More CRT-NP-S1 + Cur was observed in the brain, further indicating that CRT increased the penetration of PLGA NPs into the brain. B and C were reprinted from Huang et al. (2017). (D) The synthetic process and chemical structure of (polyol-ox)-PLGA. It can form the nanocarrier system (R@(ox-PLGA)-KcD) for the targeted release of drugs in the high-level ROS microenvironment in the brain of AD. (E) Relative ROS and TNF-a levels in the brains and IFN-γ levels in the serum of B6-Tg AD mice. R@(ox-PLGA)-KcD significantly alleviated neuro-oxidative stress and inflammation in AD. Data are presented as mean ± SD (n = 6). *P < 0.05, **P < 0.01, *vs.* AD group. (F) Representative swimming routes and route thermal maps of R@(ox-PLGA)-KcD-administered mice in the MWM. Cognitive abilities were significantly improved in the treatment group. D–F were reprinted from Lei et al. (2021). AD: Alzheimer's disease; Cur: curcumin; CRT: cyclic CRTIGPSVC peptide; INF-γ: interferon-γ; NP: nanoparticle; PEG: poly(ethylene glycol); PLGA: poly(lactic-co-glycolic acid); ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α; WT: wild type.

carrier, CS can also be the surface modifier for other nanocarriers. Results of *in vitro* experiments showed that CS modification significantly enhanced the stability and penetration of BBB of PLGA NPs (Jaruszewski et al., 2012).

Micelles/polymersomes
Micelles/polymersomes are self-assembled from amphiphilic block copolymers in an aqueous solution at concentrations higher than the critical micelle concentration (**Figure 7A**). The micelles are mainly loaded with hydrophobic agents, while the polymers can be concurrently loaded with hydrophilic agents (Kuperkar et al., 2022). Micelles/polymersomes exhibit high stability and enable sustained drug release on the basis of high drug-loading capacity. The common amphiphilic block copolymers for synthesizing micelles/polymersomes include PEG-PLGA, poly(ethylene glycol)-poly(lactic acid) (PEG-PLA), and poly(ethylene glycol)-poly(caprolactone). Their morphology is related to their properties (molar mass, ratio of blocks) and solution conditions (components, temperature, pH, charge) (Kuperkar et al., 2022).

PLGA-PEG NPs enhanced the anti-inflammatory and anti-oxidative stress effects of anthocyanins. Cellular experiments showed that PLGA-PEG NPs loaded with anthocyanins were much more protective against Aβ-induced neurotoxicity than the equivalent concentration of free anthocyanins, and that the neuroprotective effect of 50 μg effective concentration of PLGA-PEG NPs was similar to that of 200 μg free anthocyanins (Amin et al., 2017). PLGA-PEG copolymer was modified by B6 peptide to form PLGA-PEG-B6, and PLGA-PEG-B6/Cur micelles were prepared by the solvent evaporation method (Fan et al., 2018). Moreover, PLGA-PEG-B6/Cur micelles significantly improved cognitive impairment and reduced the production of Aβ and phosphorylation of tau compared to Cur and unmodified nanocarriers in APP/PS1 mice (Fan et al., 2018). Similarly, the highest concentration of lactoferrin-coupled PLGA-PEG polymersomes in the brain can reach up to 3.32 times that of the unmodified ones (**Figure 7B–D**; Yu et al., 2012). Besides PLGA-PEG micelles, PEG-PLA micelles is also a drug delivery carrier. After oral administration of PEG-PLA micelle-loaded Cur , the concentrations and mean residence time of Cur in the brain of Tg2576 transgenic mice were six-times higher than those of oral free Cur and significantly ameliorated cognitive impairment (Cheng et al., 2013).

The encapsulation efficiency of PLA-PEG micelles for Cur can reach almost 100% and are highly stable and can be stored under prolonged frozen conditions without affecting the encapsulation efficiency and chemical structure (Cheng et al., 2013). Likewise, PLA-PEG micelles were able to retain flurbiprofen at a rate of > 80% and significantly improved the ability to penetrate the BBB after modification with FB4 (mouse Tf receptor-specific RNA aptamer) in one study, implying that they can deliver effective concentrations of flurbiprofen into the CNS (Mu et al., 2013). Thus, specific surface modifications could also enhance the ability of PLA-PEG micelles to deliver agents to the brain. In an *in vitro* BBB model, the cellular uptake of B6 peptide-modified PLA-PEG micelles (B6-NP) at 37°C was approximately 2.65, 2.49, 2.46, 2.53, and 2.33 times higher than that of unmodified PLA-PEG carriers at concentrations of 100, 200, 300, 400, and 600 μg/mL, respectively, and approximately 2.75, 2.55, 2.91, 2.87, and 2.67 times higher at 4°C; whereas, in *in vivo* experiments, stronger brain enrichment of B6-NP was observed (Liu et al., 2013b). One study conducted a dual modification of PLA-PEG nanocarriers by Tf receptor monoclonal antibody (OX26) on the basis of lactoferrin-modified PLA-PEG micelles to further improve the ability of the carrier to penetrate the BBB (Li et al., 2020). In addition to targeting the known surface receptors of BBB, TGN peptide (TGNYKALHPHNG), targeting BBB screened by phage display, modified PEG-PLA NPs and showed a nearly 1.82–2.25 times higher BBB penetration capacity than unmodified carriers (Zhang et al., 2014). Recently, a study linked PEG with poly(caprolactone) by the ROS-sensitive sulfur ether cross linker, and then coupled it with the RAGE antagonist peptide (a specific ligand for RAGE) to finally self-assembly with tacrolimus (FK506) and ibuprofen to form Ibu&FK@RNPs (He et al., 2022). Ibu&FK@RNPs significantly increased the levels of the drugs in the brain (**Figure 7E**). After the administration of Ibu&FK@RNPs for 21 days, the synaptic density and Morris water maze results of APP/PS1 mice were similar to those of wild controls (**Figure 7F**). The levels of NF-κB and IL-1β in the brains of the Ibu&FK@RNPs group were 36% and 21% lower than those in APP/PS1 mice, respectively (**Figure 7G**), while the activation rate of astrocytes and Aβ burden was 7% and 60% of the untreated group, respectively. In addition, all post-treatment outcomes were significantly better in the Ibu&FK@RNPs group than Ibu&FK@NPs group (non-RAP peptide modification) (He et al., 2022).

Dendrimers
Dendrimers are polymers with highly branched structures and tunable peripheral functional groups. The hydrophobic internal space and the abundance of functional groups provide dendrimers with unique functions, such as the binding sites for drugs, nucleic acids, proteins, or functionalized ligands (**Figure 8A**). Dendrimers are mostly spherical or disc-like structures, and their morphology is influenced by the size and surface functional groups, which increase with each growing generation (Fana et al., 2020). In the case of PAMAM dendrimers, the number of functional groups on the surface of the polymer increases 2-fold with each generation from 4 in the 0^{th} generation to 64 in the 4^{th} generation, while the shape evolves from relatively asymmetric at the beginning to highly spherical in the 5^{th} and 7^{th} generations (Fana et al., 2020). Moreover, PAMAM and poly(propylene imine) polymers have been found to bind and inhibit the aggregation of Aβ on their own (Aliev et al., 2019). Hydroxy-capped PAMAM dendrimers (G4-OH) more easily penetrated the impaired BBB and targeted the neuroinflammatory microenvironment (**Figure 8B** and **C**). The vast majority of G4-OH was present in the activated glial zone in the periventricular region of the cerebral palsy rabbit model at 4 hours after intravenous administration, whereas the G3.5-COOH was not detected until 24 hours (Nance et al., 2016). On this basis, coupling N-acetyl-L-cysteine to a portion of the terminal functional groups of G4-OH (D-NAC) via disulfide bonds significantly enhanced the efficacy of N-acetyl-L-cysteine in inhibiting pro-inflammatory microglia in the brains of rabbits with cerebral palsy. D-NAC resulted in a 3.5-fold reduction in NF-κB expression compared to an equivalent dose of free drug and a more pronounced improvement in the motor function of subjects (Kannan et al., 2012).

The PAMAM dendrimers with targeted modifications also exhibited a greater ability to penetrate the BBB. Lactoferrin-modified G3-NH2 loaded with rivastigmine showed 8- and 4.2-time higher concentrations in the rat brain at 4 hours after administration than the free drug and unmodified carriers, respectively (**Figure 8D–F**). The overall mobility and memory of rats were enhanced (Gothwal et al., 2018). In addition to PAMAM, one study prepared low-generation (G0 and G1) lysine dendrimers by solid-phase peptide synthesis and successfully incorporated flurbiprofen during the synthesis to form G0K-FP and G1K-FP (Al-Azzawi et al., 2018). Compared to free flurbiprofen, G0K-FP and G1K-FP increased penetration by 12–14% in an *in vitro* BBB model (Al-Azzawi et al., 2018). Further, lysine dendrimers modified with ApoA-I (the major component of high-density lipoprotein targeting scavenger receptors on the BBB) and NL4 (the peptide targeting neurons) could effectively penetrate the BBB model and deliver BACE1 siRNA to PC12 neuronal cells, thereby downregulating the expression of BACE1 (Zhang et al., 2017a). In a recent study, a multi-targeted dendrimer APBP, which consisted of an 8-arm hydroxylated PEG linked to the ROS-sensitive alkyne group followed by binding to phosphorylated nuclear factor E2-related factor 2 (Nrf2) (activating the Nrf2-mediated signaling pathway) with modification by Aβ peptide (RAGE ligand), could target the inflammatory microenvironment of AD effectively to reduce neuroinflammation and ROS after penetrating the BBB and modulating the activated phenotype of microglia, thereby reducing Aβ burden and improving cognitive function in an AD mouse model (Liu et al., 2021b). Dendrimers are a very promising category of brain-targeting drug delivery vehicles owing to their high capacity of drug loading and amenability of modification; however, special attention should be paid to their possible cytotoxicity with an increasing number of branches.

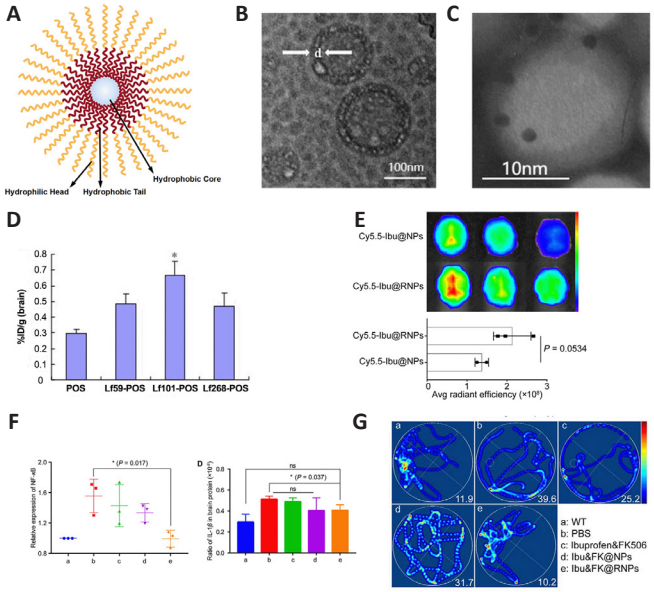

Figure 7 | The general structure of micelles and their potential as carriers for the treatment of Alzheimer's disease.

(A) Schematic diagram of the basic structure of micelles. (B) Cryogenic TEM of Lf-PLGA-PEG polymersomes. Lf-PLGA-PEG polymersomes are hollow vesicles with outer membranes formed by amphiphilic copolymers. D = 10 nm. (C) TEM image of Lf-PLGA-PEG polymersomes. The coupling between Lf and PLGA-PEG polymersomes was demonstrated by the binding of primary antibody to secondary antibody labeled with colloidal gold. (D) The brain transport capacity of polymersomes at different ratios of Lf/PLGA-PEG. Brain tissue for Lf101-PLGA-PEG polymersomes was 3.32-fold higher than that for PLGA-PEG polymersomes (*P < 0.05). B–D were reprinted from Yu et al. (2012). Copyright 2011, Springer Science Business Media, LLC. (E) Imaging of the brain at 6 hours after administration of RNPs and unmodified PEG-PLA nanoparticles in mice. Semi-quantitative analysis showed that RNPs were 1.55-fold higher than the NPs group. (F) Semi-quantitative integration intensity of NF-κB and IL-1β expression in the brain. Neuroinflammation was significantly attenuated in the RNPs-treated group. (G) Morris water maze test. The numbers at the bottom right indicate the mean time (in minutes) for mice to reach the platform. This result indicated that the cognitive function of AD mice in the RNPs treatment group was significantly improved compared to that in the other groups. Data are presented as mean ± SD (n = 3). E–G were reprinted from He et al. (2022). Avg: Average; cy5.5: cyanine5.5; FK(506): tacrolimus; Ibu: ibuprofen; %ID: the percent of injected dose; IL-1β: interleukin-1β; Lf: lactoferrin; NF-κB: nuclear factor kappa B; NP: nanoparticle; PEG: poly(ethylene glycol); PBS: phosphate buffered saline; PLGA: poly(lactic-co-glycolic acid); POS: polymersomes; RNP: RAP peptide-modified nanoparticle; WT: wild type.

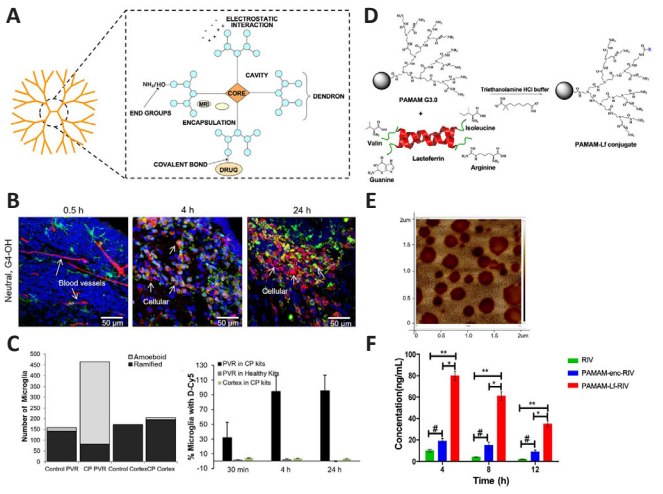

Figure 8 | The basic structure of dendrimers and their ability to penetrate the blood-brain barrier.

(A) Schematic illustration of dendrimers. Dendrimers can serve as carriers for a variety of substances including many therapeutic and diagnostic agents. Adapted from Aliev et al. (2019). (B, C) Localization and retention of PAMAM G4-OH (red) in activated glial cells (green) in the rabbit model of CP. (B) Immunofluorescence analysis of PAMAM G4-OH was able to leave the vasculature after 4 hours and rapidly localize in activated glial cells. (C) Explicit activation of microglia in the PVR of CP rabbit model. Semi-quantitative analysis from 0.5 hours to 4 hours after administration indicated that the proportion of Iba-1$^+$ microglia containing PAMAM G4-OH in the PVR of the CP rabbit model reached up to 90%, implying that G4-OH can target sites of neuroinflammation. B and C were reprinted from Nance et al. (2016). Copyright 2016 Elsevier Ltd. All rights reserved. (D) Schematic illustration of Lf-modified G3-NH2. (E) Atomic force microscopy image of Lf-G3 showed that the surface of Lf-G3-NH2 was rough, which confirmed the conjugation of Lf. (F) Rivastigmine concentrations in the brain at 4, 8, and 12 hours after intravenous administration suggested that Lf-G3-NH2 had higher bioavailability and improved retention time of rivastigmine. D–F were reprinted from Gothwal et al. (2018). Copyright 2018, American Chemical Society. CP: Cerebral palsy; cy5: cyanine5; enc: encapsulated; Iba-1: ionized calcium-binding adapter molecule 1; Lf: lactoferrin; MRI: magnetic resonance imaging; PAMAM: polyamidoamine; PVR: periventricular region; RIV: rivastigmine.

Nanogels

Nanogels (NGs) are defined as nanoscale hydrogels, that are three-dimensional polymer networks formed by physical or chemical cross-linking and have the characteristics of both hydrogels and NPs (**Figure 9A**; Zhang et al., 2016). Swelling is the most important property of NGs and can be triggered by physicochemical changes such as temperature, pressure, pH, ions, and specific molecular recognition. Nanogels are gaining increasing attention as drug-delivery carriers owing to their excellent drug-loading capacity, high stability, biocompatibility, and controlled release of drugs through controlled swelling (Zhang et al., 2016). One study prepared poly(N-vinylpyrrolidone)-co-acrylic acid NG by the ionizing radiation method and then coupled it with insulin to obtain NG-In. *In vitro* experiments showed that the NG-In was more efficient than free insulin in penetrating the BBB model (**Figure 9B** and **C**), and it activated Akt at almost twice the level of the equivalent quantity of free insulin, completely reversing the Aβ-induced cytotoxicity (Picone et al., 2016). Another study designed angiopep-2-modified CS NGs to deliver oxytocin to the brain to treat AD in the early stage. Angiopep-2-modified CS NGs can be enriched in brain regions with AD-like pathologies and effectively inhibit the activation of microglia and reduce the levels of inflammatory cytokines by blocking NF-κB and MAPK-related signaling pathways (Ye et al., 2022). Regular treatment of APP/PS1 mice with angiopep-2-modified CS NGs starting at age 12 weeks decelerated the progression of Aβ deposition and neuronal apoptosis, and prevented cognitive impairment and delayed hippocampal atrophy (Ye et al., 2022). As drug delivery carriers, the hydration layer of the NGs can inhibit the conformational transition to β-sheet in Aβ and thus reduce its neurotoxicity. However, some loaded drugs can disrupt the hydration layer (**Figure 9D**; Zhao et al., 2019). Therefore, for better synergy between NGs and loaded drugs to produce better outcomes for the treatment of AD, it is required to pay attention to adequately protect the hydration layer or enhance hydration in designing the NG formula.

Nanoemulsions

Nanoemulsions are nanoscale (< 500 nm in diameter) emulsions formed by mutually immiscible liquids after stabilization of droplets (dispersed phase) by appropriate surfactants, and are mainly divided into the oil-in-water (O/W, oil or lipid droplets in the aqueous phase) and water-in-oil (water droplets in the continuous oil phase) types (**Figure 10A** and **B**; Singh et al., 2017). In the field of drug delivery to the brain, O/W are the most widely studied type of nanoemulsions, as they contribute to the solubility and stability of lipophilic drugs and improve drug absorption in the gastrointestinal tract (**Figure 10C**), and are suitable for oral, nasal, intravenous, and other drug delivery methods. O/W nanoemulsions loaded with chrysin (chrysin-NE), which was prepared with edible oil as the oil phase, had an encapsulation efficiency of 100.29 ± 0.53% and could be stored stably at 25°C for 5 weeks (Ting et al., 2021). The nanoemulsions did not affect the inhibitory activity of chrysin for acetylcholinesterase. Interestingly, chrysin-NE inhibited butyrylcholinesterase more efficiently than free chrysin, suggesting that the components of the nanoemulsions themselves may have some pharmacological effects (Ting et al., 2021). One study prepared O/W nanoemulsions with propylene glycol mono-caprylate (capyrol 90) as the oil phase and Tween-20 as the surfactant to encapsulate naringenin, and confirmed that low-dose naringenin nanoemulsions were superior to high-dose free naringenin in inhibiting Aβ-induced oxidative damage in SH-SY5Y cells (Md et al., 2018). Similarly, in cellular experiments, RA-encapsulated O/W nanoemulsions and CS-coating RA-encapsulated O/W nanoemulsions (RA CNE) prepared with medium-chain triglyceride as droplet component and egg lecithin as surfactant by spontaneous emulsification increased the total thiol content of LPS-induced rat astrocytes by approximately 50%, and inhibited cellular production of ROS to control levels (Fachel et al., 2020a). Based on experiments in Wistar rats confirming the efficacy and safety of RA CNE *in vitro*, intranasal administration of RA CNE and RA clearly alleviated LPS-induced oxidative stress and astrocyte activation, and increased the ability of RA CNE to improve memory deficits. The effect was superior to that of free RA, probably due to the adhesion properties of CS that reduced the clearance of NPs in the nasal cavity and nanoemulsions prolonged the release and permeation time of the drug (Fachel et al., 2020b). Another experiment showed that resveratrol nanoemulsions administered intragastrically at 24 hours preoperatively can directly interact with the CNS and contribute to the alleviation of cognitive impairment and hippocampal inflammation levels (IL-1β and TNF-α) in rats after abdominal surgery (**Figure 10D**) (Locatelli et al., 2018). Therefore, compared to other nanoparticles, nanoemulsions may be suitable for oral administration, thereby broadening the delivery mode of nanocarriers for clinical application, but further research is needed.

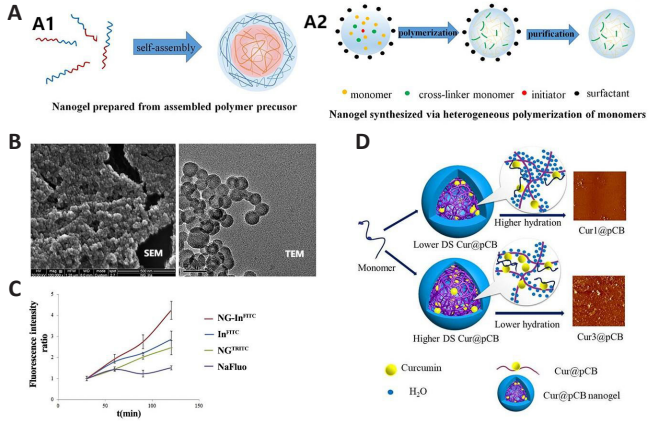

Figure 9 | **Preparation of nanogels and prospects for the treatment of Alzheimer's disease.**

(A) Synthesis methods of nanogels. (A1) Polymer precursor method, (A2) heterogeneous polymerization of monomers. Physical crosslinking (amphiphilic crosslinking, electrostatic crosslinking) usually occurs between polymer precursors with specific properties, while chemical crosslinking (formation of covalent or hydrogen bonds) can be formed with polymer precursors and monomers. Reprinted from Zhang et al. (2016). Copyright 2015 Elsevier B.V. All rights reserved. (B) Morphological analysis of NG-In. SEM and TEM confirmed the uniform distribution of the NG-In particle size. (C) The ability of NG to cross the BBB. NG-In has a higher BBB transport capacity than NG, which can be attributed to InR-mediated transport. B and C were reprinted from Picone et al. (2016). Copyright 2015 Elsevier B.V. All rights reserved. (D) Mechanism of inhibition of the Aβ fibrillation transition by the nanogel hydration layer. Low curcumin substitution (DS) disrupts the nanogel hydration layer less and has a higher inhibitory effect on fibering. Reprinted with permission from Zhao et al. (2019). Copyright 2019, American Chemical Society. BBB: Blood-brain barrier; Cur: curcumin; DS: degrees of substitution; FITC: fluorescein isothiocyanate; In: insulin; NG: nanogel; NaFluo: sodium fluorescein; pCB: poly(carboxybetaine methacrylate); SEM: scanning electron microscope; TEM: transmission electron microscope; TRITC: tetramethylrhodamine isothiocyanate mixed isomers.

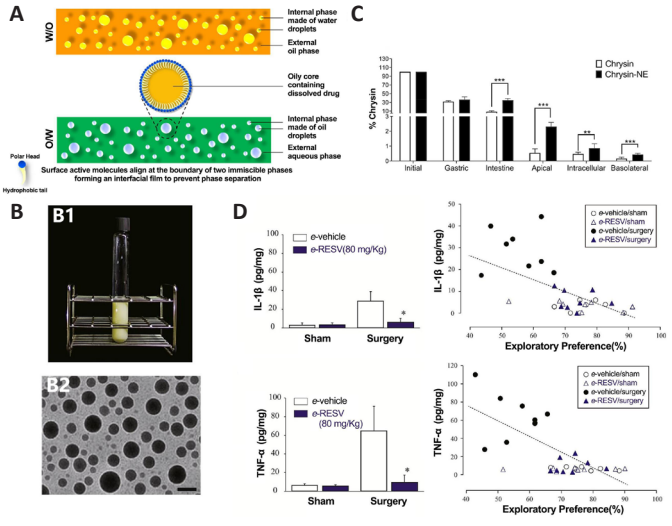

Figure 10 | **Structure and application prospects of nanoemulsions.**

(A) O/W or W/O nanoemulsion. Nanoemulsions are immiscible biphasic systems where the drug is usually dissolved in the internal phase. Reprinted with Singh et al. (2017). Copyright 2017, Elsevier B.V. All rights reserved. (B) The appearance of nanoemulsions (B1) and TEM image (B2). Nanoemulsions have a milky appearance and a spherical morphology under TEM on a scale of 100 nm. (C) Gastrointestinal effects on the bioaccessibility and absorption of chrysin and chrysin NE. NE protects chrysin from intestinal digestion and increases chrysin absorption by 2–3-fold. Reprinted from Ting et al. (2021). (D) Levels of pro-inflammatory cytokines in the hippocampus of tested rats and corresponding cognitive abilities. Prophylactic administration of resveratrol NE to rats before abdominal surgery significantly reduced inflammatory factor levels in the hippocampus and improved cognitive performance (the degree of inflammation was inversely correlated with cognitive function, with R^2 values of –0.692 and –0.709 for IL-1β and TNF-α, respectively). B and D were reprinted from Locatelli et al. (2018). IL-1β: Interleukin-1β; NE: nanoemulsion; O/W: oil-in-water; RESV: resveratrol; TEM: transmission electron microscope; TNF-α: tumor necrosis factor-α; W/O: water-in-oil.

Inorganic nanoparticles

Inorganic materials such as gold and silicon dioxide have a unique set of physicochemical properties and structural ability to form nanoparticles with characteristics such as high surface-to-volume ratio, long-term stability, and optical response, thus providing more options for precise delivery of drugs such as small molecules, nucleic acids, and proteins (Luther et al., 2020). Various inorganic NPs have been widely applied in the diagnosis and treatment of diseases such as tumors and infections, while for neurodegenerative diseases such as AD, some inorganic NPs have also shown profound potential for improving treatment and diagnosis.

Gold nanoparticles (AuNPs) are the most commonly used inorganic nanocarriers for AD treatment with the advantages of non-toxicity, tunable size and shape, and optical reactivity (Luther et al., 2020). Negatively charged AuNPs induced Aβ monomers to form fibril fragments and oligomers, thereby attenuating the toxicity of Aβ to human neuroblastoma (BE-(2)-C) cells. In addition, AuNPs preferentially bind to performed Aβ fibrils and lead to the transition of the morphology of mature fibers to amorphous aggregates and oligomers (**Figure 11A**; Liao et al., 2012). Other than inducing morphological changes in Aβ, AuNPs can protect neuronal cells from toxin injury through mitochondrial protection and anti-inflammatory effects (**Figure 11B** and **C**) (Chiang et al., 2020, 2021). *In vitro*, gold nanoclusters mitigated inflammation-induced neuronal injury in a dose-dependent manner by inhibiting the activation of the NF-κB and p38 pathway and reducing IL-6, TNF-α, and NO secretion from activated BV-2 microglia (Yuan et al., 2019). In AD mouse models, intraperitoneal administration of AuNPs significantly improved cognitive impairment and reduced oxidative stress (increased superoxide dismutase and glutathione) and inflammatory conditions (decreased NF-κB and IL-1β and increased IL-4) in the CNS (Muller et al., 2017; Dos Santos Tramontin et al., 2020). As nanocarriers, AuNPs can conjugate various therapeutic agents on the surface. One study designed multifunctional nanoagents AuNPs@POMD-pep (POMD: polyoxometalate with Wells-Dawson structure that can inhibit Aβ aggregation, pep: LPFFD peptide that can promote Aβ fibril disassembly) targeting Aβ for AD based on AuNPs (Gao et al., 2015). *In vitro*, AuNPs@POMD-pep alleviated Aβ-induced oxidative stress and cytotoxicity through the synergistic effects of inhibition of Aβ aggregation and dissociation of Aβ fibrils, while in experimental mice, AuNPs@POMD-pep effectively crossed the BBB after intravenous administration and exerted its functions in the cerebrum (Gao et al., 2015). PEG-AuNP coupling with anthocyanins (An-PEG-AuNPs) also enhanced the efficacy of anthocyanins in improving cognitive deficits in $A\beta_{1-42}$-induced AD mouse models and significantly attenuated pathological changes (Aβ burden, tau phosphorylation, and neuronal injury) in AD (Ali et al., 2017). Concurrently, An-PEG-AuNPs inhibited $A\beta_{1-42}$-induced inflammation both *in vivo* and *in vitro* (**Figure 11D–G**) and reduced microglia and astrocyte activation in Aβ1-42-treated mice (Kim et al., 2017). In addition, gold nanoclusters-conjugated berberine (BRB-AuNCs) can promote the transition of mouse mononuclear macrophage leukemia cells (RAW 264.7 cells) from M1 to M2 phenotype, thereby exerting anti-inflammatory and neuronal protective effects *in vivo* (Zhou et al., 2022). In addition to conjugating drugs to the surface of AuNPs, encapsulating them in hollow AuNPs can also improve the dissolving rate and solubility of poorly water-soluble natural compounds (Meng et al., 2016). Gold is generally considered non-toxic, but AuNPs < 5 nm can penetrate the nuclear membrane and hence bind to DNA. Therefore, more studies are needed to validate the biotoxicity of different sizes and shapes of AuNPs as well as their *in vivo* stability and effectiveness.

Mesoporous silica NPs are nanocarriers with ordered internal mesopores (typically about 2–6 nm wide) and have characteristics such as robustness and ease of surface modification, making them an ideal platform for designing multifunctional targeted and controlled release nanosystems (Vallet-Regí et al., 2017). An MSN-based vector system, Cur@MSN-RhoG/TAT involves multiple designs targeting the CNS for synergistic delivery of Cur (loaded in the internal mesopores) and plasmid RhoG-DsRed/TAT for neurite growth (loaded on the surface of MSN and controlling the release of Cur) (Cheng et al., 2019). Cur@MSN-RhoG/TAT successfully delivered Cur to protect N2a cells from paraquat-induced oxidative stress and enhanced neurite growth through synergistic effects of RhoG (Cheng et al., 2019). However, there are relatively few studies on BBB transportation of MSN. It has been shown that unmodified MSN mediates the transmission of BBB in a charge- and size-dependent manner (Chen et al., 2022). Silica-based delivery systems are promising nanocarriers for the treatment of neurodegenerative diseases such as AD, but the issue to be considered for their application in the CNS is their neurotoxicity. Exposure to SiNPs led to oxidative stress and apoptosis of SK-N-SH and N2a cells in a dose-dependent manner, while inducing pathological features of AD such as Aβ production and tau phosphorylation (Yang et al., 2014). Therefore, how to safely apply SiNPs for drug delivery to the CNS requires further exploration.

The cerium in the ceric dioxide nanoparticles (CeO_2NPs) can cycle between Ce^{4+} and Ce^{3+} and can eliminate superoxide. This property makes CeO_2NPs a very promising nanocarrier for the treatment of AD. CeO_2NPs co-incubated with primary rat cortical neurons can accumulate alongside mitochondria and prevent Aβ-induced mitochondrial disruption and cell death (Dowding et al., 2014). After being coated by PEG and then conjugated with Aβ antibody, CeO_2NPs targeted Aβ aggregates to protect neurons from Aβ-mediated cytotoxicity and significantly improved neuronal survival (Cimini et al., 2012). A recent study has shown that CeO_2NPs can attenuate oxidative stress and prevent neuronal degeneration by increasing superoxide dismutase activity and mRNA expression of key autophagy genes—ATG1 and ATG18 (Sundararajan et al., 2021).

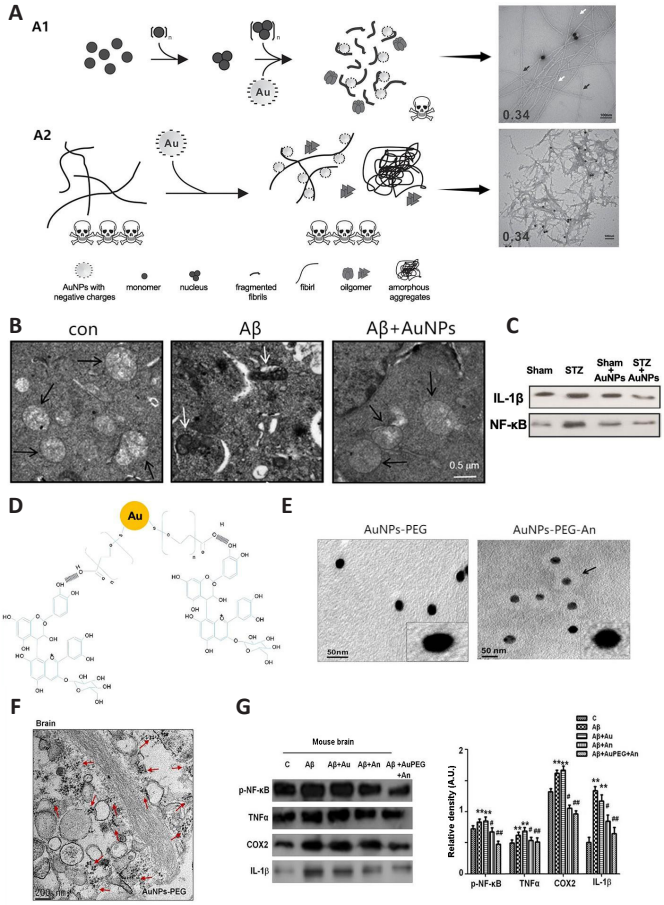

Figure 11 | **The therapeutic effect of AuNPs on AD.**
(A) Mechanistic illustration of AuNPs as therapeutic and diagnostic agents for AD. (a) AuNPs with negative surface potential prevent the formation of Aβ mature fibers, (b) AuNPs induce Aβ mature fibrils to form amorphous aggregates, although this does not significantly alter their toxicity. However, AuNPs can be used as a diagnostic tool for AD. White arrows are oligomers, black arrows are broken Aβ fibrils, and black spots are AuNPs. Reprinted from Liao et al. (2012). Copyright 2012, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission. (B) TEM images of mitochondria after AuNPs treatment. Fragments of mitochondria (white arrows) are restored to normal (black arrows) after treatment. Reprinted from Chiang et al. (2020). Copyright 2020 IBRO. Published by Elsevier Ltd. All rights reserved. (C) Western blot of inflammatory factors. Intraperitoneal administration of AuNPs decreases the expression of IL-6 and NF-κB in the brains of STZ-induced AD rats. Reprinted from Muller et al. (2017). Copyright 2017, Elsevier B.V. All rights reserved. (D) Schematic illustration of AuNPs-PEG loaded with anthocyanins. Reprinted from Ali et al. (2017). Copyright 2016, Springer Science Business Media New York. (E) TEM of AuNPs-PEG and AuNPs-PEG-An. AuNPs-PEG are round and AuNPs-PEG-An have clearly visible circles around it (black arrows). (F) TEM of a mouse brain specimen. AuNPs-PEG-An (red arrows) successfully cross the BBB and are internalized into the brain. (G) Western blot of pro-inflammatory factors in the mouse brain. Both AuNPs-PEG-An and AuNPs-PEG significantly attenuate neuroinflammation in AD mice. Data were expressed as the mean±SEM (n = 10 mice/group). *P < 0.01, vs. wild control group; #P < 0.05, ##P < 0.01, vs. $A\beta_{1-42}$-treated group. E–G were reprinted from Kim et al. (2017). Copyright @ 2017, Elsevier Inc. All rights reserved. AD: Alzheimer's disease; An: anthocyanidin; Aβ: amyloid-β; BBB: blood-brain barrier; COX2: cyclooxygenase 2; IL-1β: interleukin-1β; NF-κB: nuclear factor kappa B; NP: nanoparticle; p-NF-κB: phosphorylated NF-κB; PEG: poly(ethylene glycol); STZ: streptozotocin; TEM: transmission electron microscope; TNF-α: tumor necrosis factor-α.

Translation to Clinical Applications

The following are the main advantages of biomaterials in drug delivery for CNS diseases: 1) increasing the biological stability and blood circulation time of agents; 2) assisting drugs to cross the BBB and enhancing the penetration efficiency and targeting lesion sites through special modifications; 3) changing the release pattern of drugs and prolonging the retention time of drugs in the CNS; 4) besides playing the function of carriers, some NPs also have pharmacological effects and can play the therapeutic role synergistically with the loaded agents.

The development of multifunctional modifications or novel nanomaterials is essential, but one issue that remains to be addressed from the laboratory to clinical application is the route of administration. Currently, most nanocarriers in experiments on AD animal models are administered intravenously. Intravenous administration has the advantages of rapid onset of action and high drug utilization, but it depends on professional operation, so the economy and compliance are relatively poor, especially for the special group of AD. Therefore, oral administration in a safe, tolerable, economical, and convenient manner should be given priority. However, changes in pH, surfactants such as bile acids, and various digestive enzymes in the gastrointestinal fluid all compromise the structural integrity of NPs after oral administration (Wang et al., 2020). Stearic acid-SLN can maintain a stable particle size after 2 hours of incubation in simulated gastric juice, while after 2 hours of incubation in intestinal fluid at pH 6.8, the particle size increased by about 1.5–2 times in both the presence and absence of pancreatin, suggesting the pH-related aggregation process of NPs (Laserra et al., 2015).

The particle size of chrysin-NE in the simulated intestinal environment is also about 10-times larger than the initial size (Ting et al., 2021). Despite this, nanocarriers still significantly improve the bio accessibility of loaded drugs. In addition to the chemical environment of the gastrointestinal tract, the physical barrier is also an issue that needs to be addressed after oral administration. The uptake efficiency in the gastrointestinal tract is inversely proportional to the diameter of the NPs and is related to the shape of the NPs (Wang et al., 2020). However, there are no clear conclusions about the relationship between the morphology of NPs and cellular uptake efficiency. Additionally, the surface properties of NPs are also involved with their efficiency to penetrate the intestinal mucosa. Nanoparticles coated with hydrophilic substances such as PEG or neutral NPs with a dense charge possess a hydrophilic surface which reduces the hydrophobic interaction with the mucus thus facilitating mucus penetration. The mucosal adhesion property of CS increases the cellular transport capacity of its modified NPs. Moreover, the modification of specific ligands also enhances uptake and transport by intestinal epithelial cells (Wang et al., 2020). The absorption of orally administered drugs is a complex process, and NPs can significantly improve the bioavailability of oral drugs. However, changes in NP size and morphology in isolation cannot fully improve the intestinal transport of nanocarriers, and the effects of components, physicochemical properties, surface modification, and loaded drugs of NPs should be taken into account so that orally administered nanomedicines can be safely and effectively translated into clinical applications.

Conclusion and Perspective

Currently, no significant clinical therapeutics are available for AD. Of the multiple clinical agents targeting pathologies such as Aβ and tau, only aducanumab and lecanemab are currently approved by the U.S. FDA for clinical use. In recent decades, neuroinflammation has received increasing attention in the pathogenesis of AD, and several anti-inflammatory therapeutic agents have demonstrated their potential to modify the conditions of AD in experiments. Current anti-inflammatory strategies for AD focus on small molecule drugs such as NSAIDs, natural plant extracts, neurosteroids, and modulation of intestinal flora, while large-molecule therapeutics such as monoclonal antibodies and genetic agents are the latest emerging research hotspots. However, given the complexity of the inflammatory mechanisms in AD, a single anti-inflammatory drug has not yet been able to completely ameliorate the inflammatory changes in AD. On the basis of fully revealing the inflammatory mechanisms in AD and comparing the strengths and weaknesses of different agents, therapeutic hope can be traced from the combination of agents targeting different inflammatory pathways or the development of drugs with multiple anti-inflammatory mechanisms. In addition, the time of anti-inflammatory therapy intervention is crucial, and considerable evidence indicates that acute inflammation in the early stages is actually beneficial for AD. We assume that the progression of AD can be regarded as the outcome of the failed attempts to restore tissue homeostasis by the clearing function of acute inflammation and the subsequent chronic neuroinflammation caused by persistent disease-triggering factors. Therefore, prompt anti-inflammatory treatment may be suitable for diagnosed AD patients. We expect that the timing of anti-inflammatory interventions will be more precisely selected based on further refined assessment of AD conditions in the future.

Given the existence of the BBB, the vast majority of small molecule drugs and all large molecule drugs are blocked from the CNS, which severely hinders the pharmacological treatment of AD. To address this issue, NPs can be used to aid in drug delivery (**Figure 12**), especially for plant extracts and macromolecular drugs. All types of NPs have been demonstrated to enhance the circulating stability of drugs and, to some extent, increase the concentration of drugs in the brain. In particular, the *in vivo* stability and histocompatibility of NPs are further improved by special ligand modification, and the capability of targeting and penetrating the BBB is significantly enhanced. On the basis of the enhanced BBB penetration of NPs, precise therapeutics for AD can be realized through multiple modifications, which means that the targeted release of drugs in the inflammatory microenvironment or sites of pathological alteration in the brain can be achieved by incorporating the specifically responsive chemical bonds or secondary targeting ligands.

Although it is still in the laboratory research stage, NP-based anti-inflammatory therapy has shown great promise for the treatment of AD. Besides acting as carriers, some inorganic nanoparticles such as gold, ceric dioxide, selenium, and others, and lipid-based nanoparticles, NGs, and nanoemulsions can also produce some beneficial effects on the treatment of AD such as anti-inflammation or anti-Aβ by themselves. Furthermore, in view of the specificity of the AD population, we hope to use oral administration in clinical practice to reduce the burden on caregivers and maximize the socioeconomic benefits. However, the role of neuroinflammation in the different stages of AD has not yet been fully understood and the optimal mode of administration of different types of nanoformulations has not been fully covered in this review, which still require further extensive research.

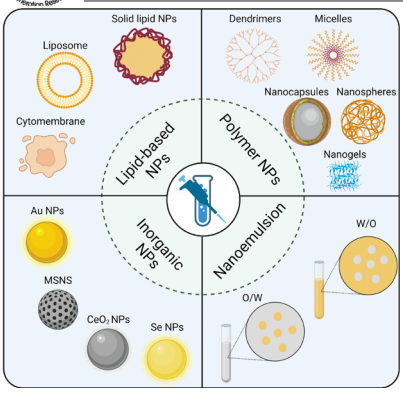

Figure 12 | Nanoparticles applied in anti-inflammatory therapy for Alzheimer's disease.
Created with BioRender.com. MSN: Mesoporous silica nanoparticle; NP: nanoparticle; O/W: oil-in-water; W/O: water-in-oil.

Author contributions: *Content and synopsis design: JC, WZ, YL, JZ, JG, YY; data retrieval: JC, WZ, YL, BG, WJ, TY, CG, DL, MH; manuscript preparation: JC, WZ, YL; manuscript review: JC, WZ, YL, BG, WJ, TY, CG, DL, MH, YY, JZ, JG; funding obtain: YY, JG. All authors have read and approved the final version of the manuscript.*
Conflicts of interest: *All authors declare no conflicts of interest.*
Data availability statement: *All data relevant to the study are included in the article or uploaded as Additional files.*

Editor's evaluation: *The review is well-documented and structured. It gave a summary of the anti-inflammatory strategies for AD (NSAIDs, neurosteroids, plant extracts, macromolecular drugs, and nanocarriers) and looked forward to the future development of anti-inflammatory strategies based on nanocarriers in the treatment of AD.*
Additional file:
Additional Table 1: *Plant extracts for anti-inflammatory treatment of Alzheimer's disease.*

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